Quality of life after breast conserving therapy and adjuvant radiotherapy for non-low risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised controlled trial

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SUMMARY

Background BIG 3-07/TROG 07.01 is an international randomised trial evaluating tumour bed boost (TBB) and hypofractionation in non-low risk ductal carcinoma *in situ* (NLR-DCIS) following breast conserving surgery and whole breast radiotherapy (WBRT). The purpose of this paper is to report the effects of diagnosis and treatment of health-related quality of life (HRQL) to two years.

Methods BIG 3-07/TROG 07.01 is a multicentre parallel randomised controlled unblinded trial. Recruitment setting was 118 hospitals in 11 countries. Women aged ≥18 years with completely excised non-low risk DCIS were randomised, unblinded, using a minimisation algorithm, to TBB (16 Gy in 8 fractions over 1.5 weeks) or no TBB, following conventional WBRT (50 Gy in 25 fractions over 5 weeks) or hypofractionated WBRT (42.5 Gy in 16 fractions over 3.5 weeks). Stratification factors were age, planned endocrine therapy and treating centre. The primary endpoint, time to local recurrence, will be reported when participants have completed 5 years of follow-up. The proposal to report the HRQL data at 2 year follow-up was approved by the Data and Safety Monitoring Committee 23/10/2015. The HRQL statistical analysis plan pre-specified eight aspects of HRQL, assessed by four questionnaires at baseline, end of treatment (EOT), and 6, 12 and 24 months after radiotherapy: fatigue, physical functioning (EORTC QLQ-C30); cosmetic status, breast-specific symptoms, arm/shoulder-related functional status (Breast Cancer Treatment Outcome Scale, BCTOS); body image and sexuality (Body Image Scale, BIS); perceived risk of invasive breast cancer (Cancer Worry Scale, CWS and a study-specific question). For each of these, TBB was compared with no TBB, and conventional with hypofractionated WBRT, using generalised estimating equation models, by intention-to-treat, with Hochberg adjustment for multiple testing. This trial is registered with ClinicalTrials.gov, number NCT00470236.

Results Between 1 June 2007 and 14 August 2013, 1208 women were enrolled and randomly assigned to receive no TBB (n=605) or TBB (n=603); 396 women were randomised between conventional (n=188) and hypofractionated WBRT (n=189). All these patients were followed up at two-year for this analysis. Most patients received their allocated treatment (1098/1208, 91%), and most completed their scheduled HRQL assessments (1147/1208, 95% at baseline; 988/1141, 87% still on study at two years). Patients with HRQL assessments at baseline and ≥1 other time point were analysed: QLQ-C30, n=1147; BCTOS, n=920; BIS, n=919; CWS, n=908; study-specific risk question, n=878. Cosmetic status was worse with TBB compared with no TBB across all time-points (global p value =0.0001, Hochberg-adjusted p=0.002); at EOT, the estimated difference between TBB and no TBB [95% confidence intervals] was 0.13 [0.06, 0.20], p=0.00021, persisting at 24 months (0.13 [0.06, 0.20], p=0.00021). Arm/shoulder function was also adversely affected by TBB (global p value =0.0033, Hochberg adjusted p=0.045); the difference between TBB and no TBB at EOT was 0.08 [0.01, 0.15], p=0.021), but considerably smaller at 24 months (0.04 [-0.03, 0.11], p=0.29). None of the other pre-specified aspects of HRQL differed significantly after adjustment for multiple testing: estimated differences between TBB and no TBB at EOT were: fatigue 1.49 [-0.81, 3.80], p=0.20; physical functioning -1.60 [-2.95, -0.24],p=0.021; breast-specific symptoms 0.15 [0.06, 0.25], p=0.002; body image/sexuality 0.22 [-0.22, 0.66), p=0.33]; CWS -0.14 [-0.38, 0.10], p=0.24), study-specific question about perceived risk of invasive breast cancer -0.11 [-0.23, 0.01], p=0.07.

Interpretation TBB was associated with persistent adverse impacts on cosmetic status and arm/shoulder functional status, which may inform shared decision making while local recurrence analysis is pending.

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RESEARCH IN CONTEXT

Evidence before this study

We searched five electronic databases: MEDLINE; PsycInfo; CINAHL; EMBASE; and Scopus from database inception to 12 November 2015. Our search strategy comprised a comprehensive set of terms for "DCIS" and "PROs" (for full list of search terms, see online Appendix A of King et al, 2017). No language restrictions were applied. We also searched the reference lists of all studies included in this review and of other relevant systematic reviews, conducted an electronic search by author of key researchers identified, and contacted experts in the field (identified by our team) to enquire about ongoing studies. We identified 19 papers that reported PROs from 13 studies. These were assessed for research quality against 21 quality assessment criteria (see online Appendix B of King et al, 2017); quality scores ranged from 19% to 69%. There were no prior meta-analyses or data from randomised trials examining PROs in patients with DCIS. Further, the quality of evidence about the impact of DCIS treatments on PROs was limited by the design, analysis and reporting of the studies. The systematic review highlighted the need for adequately powered PRO studies to assess the acute impacts, recovery trajectories and long-term deficits of contemporary treatments for DCIS.

Added value of this study

This substudy of the randomised phase III BIG 3-07/TROG 07.01 trial investigated the effects of tumour bed boost (TBB) and hypofractionation on PROs to two years after treatment in women with non-low risk DCIS treated with breast conserving surgery and whole breast radiotherapy (WBRT). To our knowledge, this is the largest prospective study of PROs in women with DCIS. Our study showed that TBB had a detrimental effect on patient-reported cosmetic outcomes and arm and shoulder functional status. The adverse effect of TBB on perceived cosmetic status persisted at 24 months whereas the effect on arm and shoulder function resolved by 24 months. These adverse effects of TBB were generally worst at the end of radiotherapy and improved over time. In contrast, adverse impacts of TBB on role, social and physical functioning were small and transient. TBB was not significantly associated with body image or perceived risk of invasive breast cancer. However, body image was markedly worse with conventionally fractionated WBRT than hypofractionated WBRT, and there was a cumulative adverse impact of radiotherapy on arm and shoulder functional status for women who received TBB after conventional WBRT.

Implications of all the available evidence

Our results provide the first body of evidence on the trajectories of impact and recovery from local therapies in patients with DCIS of the breast. Pending efficacy analysis of the effects of TBB and WBRT dose-fractionation on time to local recurrence, the primary study endpoint of BIG 3-07/TROG 07.01 trial, the PROs data presented in this report would support shared treatment decision making in DCIS for patients and clinicians.

Introduction

The impacts of treatment for invasive breast cancer on health-related quality of life (HRQL) are well documented.(1) In contrast, there is little evidence for women diagnosed with ductal carcinoma *in situ* (DCIS) of the breast. A systematic review of HRQL and patient-reported outcomes (PROs) after treatment for DCIS identified 23 papers reporting 17 studies, none of which was a RCT.(2)

Under the auspices of the Breast International Group (BIG) and led by the Trans-Tasman Radiation Oncology Group (TROG), BIG 3-07/TROG 07.01 is an international phase III RCT evaluating tumour bed boost (TBB) and whole breast radiotherapy (WBRT) dose fractionation schedules for women with non-low risk DCIS treated with breast conserving therapy.(3) The primary endpoint, time to local recurrence, will be reported when participants have completed 5 years of follow-up. A HRQL substudy provides patients' perspectives to complement the primary endpoint.

This paper reports PROs from baseline to two years after radiotherapy (RT). The primary objective of the BIG 3-07/TROG 07.01 HRQL substudy was to evaluate the impacts of TBB and WBRT dose-fractionation on key PROs that affect HRQL. Secondary objectives were to document longitudinal PRO changes, and assess variations in baseline PROs between the four participating geographic regions (Australia, New Zealand and Singapore (ANZS)); Canada; United Kingdom [UK] and Ireland; and western Europe (Netherlands,Belgium, France, Switzerland).

Methods

Study design and participants

BIG 3-07/TROG 07.01 is an multicentre parallel randomised controlled unblinded trial for patients with non-low risk DCIS. Clinical and/or pathologic markers for increased risk of local recurrence include young age (<50 years), or in patients aged ≥50 years, the presence of one or more of the following: symptomatic presentation, palpable tumour, microscopic tumour size ≥15 mm, multifocal disease, intermediate/high nuclear grade, central necrosis, comedo histology, radial surgical margin <10 mm. Women ≥18 years with non-low risk DCIS treated by breast conserving surgery and planned for post-operative WBRT were eligible for randomisation to receive TBB (16 Gy in 8 fractions over 1.5 weeks) or no TBB, following WBRT. All patients provided written informed consent before study enrolment. Ethics Committees or institutional review boards at each site approved the study protocol. Protocol amendments enabled international expansion by introducing three randomisation categories (27 August 2007) and increased the sample size from 610 to 1600 (21 December 2011). All amendments were approved by the relevant ethics committees.

Randomisation and masking

Prior to study activation, each centre elected to participate in one of three randomisation categories (Figure A). Category A was a 4-arm randomisation of TBB vs no TBB following WBRT, and conventional WBRT (50 Gy in 25 fractions over 5 weeks) vs hypofractionated WBRT (42.5 Gy in 16 fractions over 3.5 weeks)). Categories B and C were 2-arm randomisations betweenTBB vs no boost following conventional or hypofractionated WBRT, respectively.

Centralised electronic registration and randomisation was provided through a web based operating system, hosted on the University of Adelaide's Data Management and Analysis Centre (DMAC) website. Randomisation was done by dynamic allocation, using a minimisation algorithm generated by the Centre for Biostatistics and Clinical Trials, Melbourne, Victoria, Australia. Stratification factors were age at diagnosis (< 50 years, ≥ 50 years), planned endocrine therapy (yes, no) and treating centre. Neither patients nor treating staff were masked to treatment allocation.

Procedures

All patients received WBRT which was administered once daily within 12 weeks of the last breast surgical procedure. No dose modification or treatment interruption was permitted, as per the protocol. Computer tomography (CT)-based RT planning was mandatory. The WBRT was delivered using tangential photon beams with wedges or sub-fields to optimise dose homogeneity. The number of treatment visits required ranged from 16 (hypofractionated WBRT [42.5 Gy in 16 fractions], no TBB) to 33 (conventionally fractionated WBRT [50 Gy in 25 fractions] plus TBB [16 Gy in 8 fractions]). TBB, if allocated, was given after WBRT to the primary tumour site using an incident electron beam or megavoltage photons via tangential or other field arrangements that conformed to protocol-specified dose homogeneity and normal tissue constraints.

Interstitial brachytherapy was not permitted. The use of bolus over the treated breast to increase skin dose and regional nodal irradiation were also not permitted. BIG 3-07/TROG 07.01 included an RT quality assurance programme. Adjuvant endocrine therapy use was at the discretion of the treating clinicians, and chemotherapy use was prohibited.

Patients were followed up 3-6 monthly for three years after RT, and annually for a total of 10 years. Bilateral mammogram was performed one year after the pre-treatment mammogram and then annually. Patients with protocol eligibility violation would be excluded from main analysis of the randomised trial. All reported local recurrence events were centrally reviewed based on source documents. Serious adverse events including grade 4 or 5 acute or late morbidity were reported from the time of study registration until 30 days after the last RT fraction independent of whether they were protocol therapy-related. Adverse events and overall study conduct were reviewed by the Trial Steering Committee at least six monthly during the accrual phase and then annually, and monitored by the Data, Safety and Monitoring Committee at least annually.

Health-related quality of life assessment

HRQL was assessed prior to randomisation (baseline), at the end of RT (EOT) and at 6, 12, 24, 60 and 120 months after RT, and were administered during clinic attendances. HRQL was assessed using several well-validated self-reported questionnaires, listed below in relation to eight key PROs (*italisicised*) of particular relevance in this trial. At European Organisation for Research and Treatment of Cancer (EORTC sites), only the EORTC QLQ-C30 was administered. Reasons for non-completion were recorded by site staff.

Fatigue and *physical functioning* were assessed with the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30), which is valid in breast cancer.(4) Following EORTC scoring algorithms, scales ranged 0-100.(5) A high score for physical function represented a high level of function (similarly for global health status/QOL and other functional scales); whilst for fatigue (and other symptoms) a high score for a symptom scale indicated a high symptom burden.

Perceived cosmetic outcome was evaluated using the Breast Cancer Treatment Outcome Scale (BCTOS), yielding three subscales: breast-specific *cosmetic status* (BCTOS -CS), arm and shoulder-specific *functional status* (BCTOS -FS) and *breast-specific symptoms* BCTOS (-BSS),(6) each ranging 1-4. The 22 BCTOS questions ask about the perceived degree of difference between the treated versus untreated breast, with higher scores indicating greater asymmetry.

Body image and sexuality was assessed using the Body Image Scale (BIS).(7) The 10 items were summed to produce an overall summary score, ranging 0-30, with higher scores indicating worse body image and sexuality. BCTOS and BIS were both validated instruments for breast cancer.

Perceived risk of invasive breast cancer was assessed in two ways. First, using the Cancer Worry Scale (CWS),(8) modified with permission of the CWS authors by replacing the term “cancer” with “invasive cancer”. The four items were summed to produce an overall score ranging 0-16, higher scores indicating more cancer worry. Second, with a study-specific question: “In your opinion, compared with other women your age who have had DCIS, what are your chances of getting invasive breast cancer?”, based on a question used previously.(9, 10) There were five response options: much lower (1); somewhat lower (2); the same (3); somewhat higher (4); a lot higher (5).

Two additional questionnaires, the Distress thermometer and the Hospital Anxiety and Depression Scale, were removed in a protocol amendment two years after study activation due to considerations of patient burden, information redundancy and data management costs. The limited data collected are reported descriptively in Table A (supplementary appendix) given the scarcity of published PRO data in DCIS.(2)

Outcomes

The primary endpoint of the BIG 3-07/TROG 07.01 study is time to local recurrence; this will be reported when participants have completed 5 years of follow-up. Secondary endpoints are: overall survival; time to disease recurrence; cosmetic outcome; radiation toxicity; HRQL. The focus of this paper is HRQL at two years. All other secondary endpoints will be analysed and reported in subsequent papers.

HRQL is a secondary endpoint. HRQL is a multi-dimensional construct, encompassing a broad range of impacts of diagnosis and treatment on patients’ perceptions, functioning and well-being. To focus our hypotheses and reduce multiple-testing, our statistical analysis plan pre-specified eight specific PROs: fatigue, physical functioning, cosmetic status, functional status,

breast-specific symptoms, body image and sexuality, perceived risk of invasive breast cancer (assessed in two ways, as described above). These PROs were selected because they are well-established as key contributors to HRQL following treatment for early-stage invasive breast cancer.(1) We refer to these as 'key PROs'.

In addition to fatigue and physical functioning, the EORTC QLQ-C30 questionnaire assessed four other aspects of functioning (role, social, emotional, cognitive), seven other symptoms (pain, dyspnoea, insomnia, loss of appetite, nausea/vomiting, diarrhoea, constipation), financial impact, and global HRQL. These were considered exploratory PROs.

The clinical importance of PRO results from the EORTC QLQ-C30 (including fatigue and physical functioning) was determined used interpretation guidelines for differences between groups (11) and change over time (12). Since interpretation guidelines were not available for the other questionnaires, Cohen's guidelines for effect sizes was used to interpret the observed mean differences and changes in the other key PROs (13).

Statistical analyses

The sample size for the HRQL substudy was calculated a priori for the primary PRO analysis, which aimed to detect a difference between the TBB and no TBB groups. To detect a difference of 0.2 standard deviations of a PRO scale with 80% power at a two-sided alpha level of 5%, the required sample size was 790 patients. Allowing for a 5% annual attrition rate, the target sample size was 1020 patients. All patients recruited to the BIG 3-07/TROG 07.01 study were eligible for the HRQL substudy, up to the HRQL target sample size, which was smaller than the total trial sample size.

The primary PRO hypothesis was that women randomised to receive TBB following WBRT will report: more fatigue and breast-specific symptoms; poorer perceived cosmetic outcome; poorer perception of body image and sexuality; and decreased perceived risk of invasive breast cancer; compared to women who do not receive TBB. The secondary hypothesis was that women who receive hypofractionated WBRT will report less fatigue and breast symptoms than those randomised to receive conventional WBRT but the groups will not differ in arm/shoulder-related functional status, cosmetic outcome, body image and sexuality, or perceived risk of invasive breast cancer.

Analyses were conducted after the two-year HRQL data were mature due to the lack of randomised trials of DCIS reporting HRQL data and because systematic reviews of HRQL in DCIS and early stage invasive breast cancer indicate impact and recovery trajectories for relevant PROs stabilise by two years post-surgery (1, 2). Our primary PRO analysis compared TBB versus no TBB, with WBRT dose-fractionation included as a covariate. A secondary PRO analysis compared conventional versus hypofractionated WBRT, with TBB included as a covariate; limited to patients in randomisation category A only, plus a sensitivity analysis in all patients. Interactions between TBB and WBRT dose-fractionation were validly assessable only in the Category A patients.

Responses to the questionnaires were scored into scales according to their respective standard scoring algorithms. If some items were missed, the scale score was imputed from the completed items if at least 50% of the items were completed. Otherwise the score was set to missing.(5) The proportion of patients who completed HRQL assessment at each scheduled time point was calculated, and the reasons and patterns of non-completion were examined via key PRO trajectories over time stratified by dropout time to assess whether missing data was likely to be missing completely at random or not.

Each PRO (whether a key or exploratory PRO) was analysed as follows. For each PRO separately, participants with a score at baseline and at least one other time point were included. Generalised estimating equation (GEE) models were used to compare PRO scores by study arms, overall and at each assessment time point, adjusted for the respective baseline PRO levels and five pre-specified covariates [age (<50, ≥50 years), planned endocrine therapy (yes, no), geographic region (ANZS; Canada; the UK and Ireland; the rest of Western Europe), time since last surgery, number of ipsilateral breast surgical procedures] and three post-hoc covariates [tumour size (≤20mm, >20mm), nodal surgery (axillary dissection or sentinel node biopsy, neither), upper outer tumour location (yes, no)]. Assessment time points were included categorically, and differences between study arms at each time point were estimated from GEE models.

Adjustment for multiple hypothesis testing (14, 15) was confined to the 16 global tests (i.e. 8 key PROs x 2 aspects of radiotherapy, TBB and WBRT dose-fractionation); each global test assessed the difference between treatment groups across all time points from the GEE model for

specific PRO and aspect of radiotherapy. As most correlations (Spearman's) ranged 0.20-0.40, Hochberg adjustment methods were used.(16)

The clinical importance of observed differences was assessed using interpretation guidelines for the QLQ-C30(11, 12) and Cohen's effect sizes(13) for the other questionnaires.

To complement the model estimates, trajectories of change from baseline were plotted for each PRO; these were based on the raw data, and were not adjusted for covariates. For completeness, descriptive statistics including sample size, mean and standard deviation for each PRO were tabulated at each assessment time point (Table B).

To enable interpretation of the clinical importance of the six key PROs not derived from the EORTC QLQ-C30, effect size (ES) for the difference between TBB and no TBB at was calculated as the estimated difference between the groups divided by the standard deviation at baseline, with ES $\geq$ 0.20 deemed clinically important (13).

All analyses described above were pre-specified in the statistical analysis plan, approved by the Data and Safety Monitoring Committee October 23, 2015.

The statistical analysis plan stated three additional hypotheses, but did not specify corresponding statistical analyses. The first two related to differences in baseline PROs by participating geographic region and randomisation category, respectively, with corresponding hypotheses: 1) Baseline PROs were similar between geographic region; 2) Baseline PROs were similar between the three randomisation categories. These two hypotheses were examined using Kruskal-Wallis tests, and are reported in this paper. The third hypothesis was: There will be good correlation (Spearman correlation coefficient > 0.7) between PRO scores relating to patients' perceived cosmetic outcomes and EORTC cosmetic scores assessed by research staff of participating centres. Analyses regarding this hypothesis will be conducted for a future stand-alone paper.

The following post-hoc analyses were conducted. Three additional covariates were added to GEE models (see above) and the models were re-estimated; results from the final models with eight covariates are reported. To determine whether SNB status was associated with PROs, we examined the PRO data at baseline and 2 years of the 988 patients who completed questionnaires at both time times. Correlations among the eight key PROs were be estimated to inform choice of critical p-value adjustment method.

All statistical analyses were performed using SAS version 9.4, and all outcomes analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00470236.

Role of the funding source

The study funders had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author and senior author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between June 1, 2007 and August 14, 2013, the trial recruited 1208 patients to the HRQL substudy from 118 hospitals in 11 countries. All these patients were followed up at two-years for this analysis. Figure 1 shows patient flow through to PRO analysis in Categories A, B and C. The 1147 patients who completed measures at baseline and at least one other time point were included in analyses. Clinical and pathologic characteristics of the PRO analysis sample by allocation to TBB, and by fractionation schedule, are in Table 1, and by the four study arms in Tables C-D (Category A (n=377), all patients (n=1147)).

Most patients completed scheduled HRQL assessments: 1147 (95%) of 1208 patients at baseline (1147), 988 (87%) of 1141 patients still on study at two years (Table 2, QLQ-C30; Table E for other PROs). At two years, reasons for missed questionnaires included site error (42/159=26%), patient did not attend clinic (28/159=18%), inconvenient for patient (11/159=7%), patient too busy (7/159=4%), patient not interested (6/159=4%). PRO trajectories over time stratified by dropout time (Figure B) show some poorer outcomes for the small number of patients who dropped out after EOT (n=25) and after 6 months (n=20), but not for those who dropped out after 12 months (n=114). Post-hoc, we observed that the 159 patients who did not complete QOL questionnaires at two years were more likely to have had sentinel node biopsy (SNB) than those who completed 2-year questionnaires, but otherwise were similar (Table F). This difference was unlikely to introduce bias because change from baseline to two years did not differ by SNB status (Table G, post-hoc analysis of the 988

patients who completed questionnaires at both time times).

The impact of TBB was assessed in patients who completed PROs at baseline and at least one other time point (QLQ-C30, n=1147; BCTOS, n=920; BIS, n=919; CWS, n=908; Perceived Risk, n=878). Figure 2 presents the trajectory graphs for the eight key PROs. The largest differentials were observed in cosmetic and functional status (BCTOS-CS, Fig 2c; BCTOS-FS, Fig 2d); these were the only PRO scales for which the global test was statistically significant after adjusting for multiple testing (BCTOS-CS estimate [95% confidence intervals] =0.10 [0.05, 0.15], p=0.00014, Hochberg-adjusted p=0.0016; BCTOS-FS 0.08 [0.03, 0.13], p=0.0033, Hochberg-adjusted p=0.045). As Figure 2c shows, cosmetic status worsened from baseline to EOT in both TBB and no TBB groups but more so in the TBB group (0.13 [0.06, 0.19], p=0.00020). Cosmetic improvement was observed in both groups over time after RT, but a marked differential due to TBB persisted at 12 months (0.10 [0.04, 0.17], p=0.0022) and 24 months (0.13 [0.06, 0.20], p=0.00021). Figure 2d shows that arm and shoulder-related functional status also worsened from baseline to EOT in both groups, but more so in the TBB group (differences at EOT (0.08 [0.01, 0.15], p=0.021), six months (0.11 [0.03, 0.18], p=0.0045) and 12 months (0.09 [0.03, 0.16], p=0.0066)). Cosmetic and functional status of the no TBB group returned to baseline levels by 12 months, but the TBB group reported persistent asymmetry at 24 months. Regarding the clinical importance of the BCTOS results, four between-group differences (estimated from GEE models) achieved Cohen's threshold for small but clinically important effect sizes (ES): arm/shoulder functional status at 6 months (ES=0.20) (Figure 2d); cosmetic status at EOT (ES=0.22) and 24 months (ES=0.22) (Figure 2c); breast-specific symptoms at EOT (ES=0.21) (Figure 2c). All other effect sizes for the BCTOS scales and time points ranged 0.13-0.18, less than the 0.2 clinical importance threshold.

None of the other six key PROs passed the global statistical significance test, with or without Hochberg adjustments. Figures 2a, 2b and 2e-2h show their time trajectories. Estimated differences and effect sizes between TBB and no TBB at EOT for these six PROs were: fatigue 1.49 [-0.81, 3.80], p=0.20, ES=0.08; physical functioning -(-1.60 [-2.95, -0.24],p=0.021, ES=0.13; breast-specific symptoms 0.15 [0.06, 0.25], p=0.002, ES=0.22; body image/sexuality 0.22 [-0.22, 0.66], p=0.33, ES=0.05; CWS -0.14 [-0.38, 0.10], p=0.24, ES=0.06; study-specific question about perceived risk of invasive breast cancer -0.11 [-0.23, 0.01], p=0.07, ES=0.10. Of these, only breast-specific symptoms met the ES≥0.20 threshold for clinical importance.

Supplementary Figure C presents the trajectory graphs for the 13 exploratory PROs. Of these, only the EORTC QLQ-C30 role functioning scale had a global test p-value of less than 0.05 (estimate -2.36 [95% CI -3.90, -0.81], p=0.0030; not included in Hochberg adjustment as it was not a key PRO). Figure Cb shows that role functioning deteriorated from baseline to EOT in both groups but more so in the TBB group (-3.41 [-6.02, -0.80], p=0.011). While there was improvement in both groups by six months, the differential in role functioning between the groups persisted at six months (-3.12 [-5.27, -0.96], p=0.0047) with the TBB group returning to baseline level and the no TBB group improving beyond baseline level. Social functioning followed a similar pattern (-2.91 [-5.17, -0.66], p=0.011 at EOT, -2.05 [-3.79, -0.32], p=0.020 at six months; Figure Cc). However, none of these differences reached thresholds for clinical importance.(11)

The impact of WBRT dose-fractionation was assessed among patients in randomisation category A who completed PROs at baseline and at least one other time point (QLQ-C30, n=377; BCTOS, n=376; BIS, n=377; CWS, n=373; Perceived Risk, n=359), and as a sensitivity analysis, among all patients (numbers per PRO questionnaire were as for the TBB analysis, given above). None of the key PROs were statistically different in Hochberg-adjusted global tests of dose-fractionation in Category A patients. The sensitivity analysis generally yielded similar model estimates. Figures 3 and D show trajectory graphs for Category A and all patients, respectively. The only difference that was clinically important was for body image and sexuality at EOT among category A patients (-1.10 [-1.79, -0.42], p=0.002, ES=0.25, Figure 3d), with those receiving hypofractionation reporting better body image/sexuality than those receiving conventional fractionation. None of the exploratory PROs were significantly different due to WBRT dose-fractionation, either in Arm A or all patients.

There was a statistically significant interaction between TBB and WBRT dose-fractionation for only one PRO scale, BCTOS-FS (p=0.0082), suggesting that the effect of the two parameters on arm and shoulder-related function was not simply additive. As Figure E shows, TBB had a detrimental effect on arm/shoulder function for patients who received conventional WBRT but not for those who received hypofractionated

WBRT . Those randomised to receive TBB following hypofractionated WBRT or no TBB after conventional WBRT experienced approximately the same degree of arm and shoulder function loss as those who were randomised to have no TBB after hypofractionated WBRT.

There were some differences in PROs among geographic regions at baseline (Table I). Patients in Europe reported worse body image and sexuality than those in other regions ($p<0.001$); the largest difference was between Europe and ANZS (ES=0.60) and the smallest between Europe and UK/Ireland (ES=0.29). European patients had the worst perceived cosmetic status ($p=0.008$; BCTOS-CS ES=0.53). Cancer worry scores of patients in UK/Ireland were somewhat higher than other regions ($p=0.017$; ES=0.27). For the QLQ-C30, even the largest differences were in the clinically small range:(11) role functioning ($p<0.001$, 9.0 points better in Canada than Europe); dyspnoea ($p=0.0020$, 5.2 points worse in Europe than the UK/Ireland); and financial problems ($p<0.001$, 6.5 points worse in ANZS than Europe).

Results of the remaining two post-hoc analyses were as follows: 1) The inclusion three additional covariates post-hoc (tumour size, nodal surgery, upper outer tumour location) did not change results substantively. 2) Correlation between PRO scales ranged from 0.05 to 0.62 (absolute values; Table H). The highest correlations were between fatigue and physical functioning (range 0.50-0.62 across assessment time points). The perceived risk of invasive breast cancer had the lowest correlations with other PROs (range 0.02-0.18).

Discussion

Our study showed that TBB following breast conserving surgery and WBRT had a detrimental impact on patient-reported cosmetic outcomes, and arm and shoulder functional status. These impacts, evident by the end of RT, were sufficiently large to be clinically important.(11-13) The adverse effect of TBB on cosmetic status persisted at 24 months whereas the effect on arm and shoulder functional status reached a clinically relevant threshold at 6 months and resolved by 24 months. The adverse impact of TBB on role, social and physical functioning did not reach thresholds for clinical importance and resolved by 24 months. TBB was not significantly associated with body image and sexuality or perceived risk of invasive breast cancer. Body image and sexuality were markedly worse at the end of treatment with conventional WBRT as compared to hypofractionated WBRT; this differential diminished somewhat with time. There was a cumulative adverse effect on arm and shoulder functional status for women who received both TBB and conventional WBRT.

In women with invasive breast cancer, WBRT is known to cause acute symptoms of fatigue,(17, 18) and breast-specific symptoms of radiation dermatitis, pain and oedema.(17-21) Our study confirmed these same outcomes in women with DCIS and provided useful evidence about the trajectories of their impact and recovery over time. The addition of TBB to WBRT did not have a significant impact on fatigue or social functioning, and was shown to have only a small, transitory impact on breast-specific symptoms. Previous trials of TBB irradiation in patients with invasive breast cancer reported limited data on acute toxicity and PROs but demonstrated a deleterious impact of TBB on physician reported cosmetic outcomes.(22) Our findings are important as they highlight the impact of TBB not only on patient-reported cosmetic outcomes but also functional outcomes and breast-specific symptoms.

The randomised Standardisation of Breast Radiotherapy (START) trials compared a number of hypofractionated WBRT schedules with conventional WBRT in patients with invasive breast cancer.(23) These trials demonstrated that the late radiation toxicities of breast shrinkage and telangiectasia that affected cosmetic outcome were less with hypofractionated WBRT (40 Gy in 15 fractions over 3 weeks) compared to conventional WBRT (50 Gy in 25 fractions over 5 weeks). In the 2208 women who participated in their PRO study, the only PRO that differed significantly at 5 years was a change in skin appearance. Adverse change in skin appearance was significantly less for women who received 39 Gy in 13 fractions over 5 weeks or 40 Gy in 15 fractions over 3 weeks compared to those who received 50 Gy in 25 fractions.(24) Consistent with our findings, the START trials showed no evidence that hypofractionated WBRT was associated with significant differences in any other breast, arm or shoulder symptoms or body image.

In another randomised trial (n=287; 22% DCIS, 78% early breast cancer), patients allocated to hypofractionated WBRT reported less fatigue at 6 months after RT than those assigned conventional WBRT when TBB was used in both trial arms.(25) There were no differences between trial arms at 6 months or 3 years in any of the BCTOS scales or in body image.(26)

While our study showed that TBB adversely impacted perceived cosmetic status, it did not confirm the expected adverse consequence on body image and sexuality.(27) While the latter finding is consistent with evidence that women treated for DCIS experience little impact on body image,(2) the lack of association between perceived cosmetic status and body image contrasts with other studies where they were correlated.(28, 29) The lack of impact on body image and sexuality in our study might be related to psychological adaptation, or the impact on perceived cosmetic status being confined to only part of the breast while the impact on body image and sexuality was previously evaluated across interventions that affected the whole breast.

The reasons that TBB was associated with adverse arm and shoulder function after conventional WBRT were unclear. Nodal surgery is known to affect the issues covered by the BCTOS-FS items in invasive breast cancer (1) but inclusion of nodal surgery as a covariate in our post-hoc analysis did not change results substantively. The use of high tangents for WBRT could affect arm and shoulder symptoms but was unlikely to be used in patients with DCIS and differential use by TBB could not be evaluated as it was not recorded in the study database. TBB location differences between the boost or fractionation groups is unlikely to account for the finding as there were only small differences in the percentages of upper outer quadrant tumour locations. WBRT fractionation did not affect BCTOS-FS scores in Category A patients so it seems unlikely that the worse arm and shoulder function was a direct result of the use of conventional WBRT. However, some patients develop shoulder problems due to the mechanics of lifting the arms over the head to accommodate tangent and boost RT in the supine position, and one could speculate that the increased number of treatment visits and requirements for daily shoulder abduction (25+8=33 over 6.5 weeks vs. 16+8=24 over 5 weeks) might have had some effect of shoulder discomfort, but that this should have been transient and have resolved by 2 years. It is more the observation was a chance finding despite the use of randomisation, the large sample size, and adjustment for multiple hypothesis testing in this study.

Our findings did not support our hypothesis that women randomised to receive TBB would have a lower perceived risk of invasive breast cancer. Other studies found that women diagnosed with DCIS had exaggerated fears of breast cancer recurrence and dying of breast cancer, which occurred early and persisted for many years.(2) In contrast, participants of our study expressed concerns about getting invasive breast cancer at baseline but these subsided steadily and by 24 months, had been reduced by a small but clinically relevant extent (0.3 effect size).

Our study adds to knowledge about recovery trajectories in women diagnosed and treated for DCIS. The results were consistent with published studies that core aspects of HRQL were initially impacted but most returned to baseline within 24 months.(2) The degree of worsening across the core aspects of HRQL was generally small except for fatigue scores, which showed a substantial deterioration at EOT. Emotional function measured using QLQ-C30 was not adversely impacted during RT.

While several baseline PROs were statistically different between geographic regions ($P<0.05$), these were generally small and there was not a consistent pattern for one region being worse across domains. Since multiple comparisons were conducted, false positive findings were possible. Any true differences might be attributed to differences in health care practices, cultural attitudes or linguistic nuances in translation of PROs instruments.

To our knowledge, this is the first prospective PROs study conducted in a large, well-defined, homogeneously treated cohort of women with pure DCIS of the breast in an international randomised trial examining the effects of TBB and WBRT dose-fractionation schedules. Study participants were longitudinally assessed at pre-defined intervals over two years using reliable and valid instruments, PRO completion rates were high (87% at 2 years), and the reasons and patterns of non-completion suggested the missing data were generally missing completely at random, giving us confidence in the robustness of the findings.

Another study strength was that only 14% of the PRO study participants received adjuvant endocrine therapy so the reported-patient experiences were primarily a measure of the impact of their diagnosis and local therapies without the confounding effect of endocrine therapy-related toxicity. The physical effects of WBRT with or without TBB are expected to be the same for women with early-stage invasive breast cancer and women with DCIS. Therefore, the magnitude of the impacts of local therapy observed in our study could reasonably be extrapolated to patients with early-stage invasive breast cancer, and serve as a baseline for distinguishing the impact of local therapy from that

of systemic therapy during the first two years after diagnosis.

Our study had some limitations arising from a study design feature included to enhance feasibility of enrolment: each centre elected to participate in one of three randomisation categories. Only Category A involved randomisation between TBB vs no TBB and conventional WBRT vs hypofractionated WBRT, which enabled assessment of interactions between TBB and WBRT dose-fractionation, and minimised systematic bias due to institutional factors. However, this restricted sample size; a post-hoc power calculation determined that the 377 Category A patients provided 80% power at a two-sided alpha level of 5% to detect a difference between the two WBRT fractionation arms of 0.3 standard deviations, which is considered clinically significant(11). The sensitivity analyses (including patients from all randomisation categories) had a greater sample size but the potential for confounding of results by systematic differences in centres that selected conventional WBRT or hypofractionated WBRT. Local convention likely accounted for institutional variations in the use of conventional or hypofractionated WBRT, but participating clinician biases, health care system factors, and factors underlying regional difference in PRO may all have contributed towards variations. All statistical models included several covariates (age, planned endocrine therapy, time since last surgery, number of ipsilateral breast surgical procedures,tumour size, upper-outer tumour location, nodal surgery and geographic region) to adjust for any systematic differences between institutions regarding these variables in the sensitivity analyses.

There were several challenges common to PRO studies. Maintaining a pre-determined Type I error level is difficult when outcomes are correlated, and adjustments to control Type I error inflation could reduce power in detecting significant differences. Simple Bonferroni adjustment assumes that outcomes are independent, so is overly conservative when outcomes are correlated (i.e. the actual Type 1 error rate is more restrictive than intended). As the correlations in our dataset were between 0.20 and 0.40, we elected to apply the Hochberg method, as this maximizes power while controlling Type I error when correlations were in this range.(16) To avoid being overly restrictive, we confined adjustment for multiple hypothesis testing to 16 global tests including 8 key PROs and 2 sets of global hypotheses (TBB, WBRT dose-fractionation). In addition, PRO results must be interpreted in the context of clinical importance in addition to statistical significance.(14, 15) We achieved this by using available interpretation guidelines for the QLQ-C30, and well-established effect size thresholds for other PROs measures.

In conclusion, this prospective evaluation of PROs from baseline to two years in a large, international randomised trial of radiation doses and fractionation schedules following breast conserving surgery in women with DCIS showed a modest but persistent adverse impact of TBB on cosmetic and functional status while the impact on HRQL was small and transient. There was evidence to support that hypofractionated WBRT was better tolerated by patients than conventional WBRT. Longer term follow up will need to confirm the trends observed in HRQL at 2 years. In the interim, published studies evaluating the efficacy of TBB for DCIS in reducing the risks of local recurrence and salvage mastectomy rates are limited to retrospective analyses, which yielded conflicting results.(30) Until the efficacy results of BIG 3-07/TROG 07.01 are published, the PROs data serve to inform shared treatment decision-making in weighing the potential benefits against the adverse effects of TBB and WBRT fractionation schedules in the context of individualised recurrence risk assessment and patient preferences.

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Author statement

BHC, TW, IAO, IK, HW, GG and PS were involved in the study design. BHC, TW, IAO, IK, HW and GG oversaw the trial conduct. BHC, TW, IAO, IK, HW, GG and MTK were members of the BIG 3-07/TROG 07.01 Trial Steering Committee. EL and MTK prepared the statistical analysis plan, and BHC reviewed the drafts. EL performed the data analysis and wrote the statistical report. MTK, EL and BHC interpreted the data. MTK and BHC wrote the manuscript, and EL, TW, IAO, IK, HW, GG and PS reviewed the drafts. All authors gave final approval of the manuscript.

Declaration of interest

TW reports grants from Genomic Health (Canada), outside the submitted work. MTK, EKL, IAO, IK, AHW, GG, PS and BHC declare no competing interests.

Data sharing

Data sharing from this trial is governed by BIG and TROG policies. This manuscript is the two-year analysis of a secondary endpoint, with the primary endpoint based on 5-year follow-up. Data sharing will be considered when the primary endpoint is published.

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Table 1: Patient characteristics at baseline for patients included in analysis: boost vs no boost (n=1147); conventional vs hypofractionated WBRT (n=347, randomization Category A only and n=1147*, all patients)

		Tumour bed boost		WBRT dose-fractionation (Category A)		WBRT dose-fractionation (all patients)	
		No boost (N=574)	Boost (N=573)	Conventional (N=188)	Hypofractionated (N=189)	Conventional (N=615)	Hypofractionated (N=532)
Age	<50	102 (18%)	105 (18%)	37 (20%)	36 (19%)	120 (20%)	87 (16%)
	≥50	472 (82%)	468 (82%)	151 (80%)	153 (81%)	495 (80%)	445 (84%)
Region	Australia, New Zealand, Singapore	212 (37%)	215 (38%)	134 (71%)	134 (71%)	285 (46%)	142 (27%)
	Canada	117 (20%)	116 (20%)	17 (9%)	13 (7%)	51 (8%)	182 (34%)
	United Kingdom, Ireland	110 (19%)	110 (19%)	32 (17%)	37 (20%)	90 (15%)	130 (24%)
	Europe	135 (24%)	132 (23%)	5 (3%)	5 (3%)	189 (31%)	78 (15%)
Tumour location	Upper outer quadrant	201 (35%)	219 (38%)	71 (38%)	70 (37%)	224 (36%)	196 (37%)
	Upper inner quadrant	60 (10%)	52 (9%)	22 (12%)	17 (9%)	57 (9%)	55 (10%)
	3 o'clock	32 (6%)	45 (8%)	13 (7%)	7 (4%)	43 (7%)	34 (6%)
	12 o'clock	50 (9%)	39 (7%)	14 (7%)	23 (12%)	46 (7%)	43 (8%)
	Central (within 3cm radius of nipple)	65 (11%)	91 (16%)	18 (10%)	20 (11%)	90 (15%)	66 (12%)
	Lower inner quadrant	35 (6%)	32 (6%)	13 (7%)	11 (6%)	30 (5%)	37 (7%)
	Lower outer quadrant	62 (11%)	38 (7%)	13 (7%)	18 (10%)	57 (9%)	43 (8%)
	6 o'clock	27 (5%)	24 (4%)	9 (5%)	10 (5%)	23 (4%)	28 (5%)
	9 o'clock	41 (7%)	33 (6%)	15 (8%)	13 (7%)	44 (7%)	30 (6%)
Number of re-excisions following initial surgery	0	395 (69%)	382 (67%)	122 (65%)	112 (59%)	414 (67%)	363 (68%)
	1	166 (29%)	170 (30%)	58 (31%)	73 (39%)	177 (29%)	159 (30%)
	2	7 (1%)	16 (3%)	6 (3%)	2 (1%)	16 (3%)	7 (1%)
	3	3 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2 (0%)
	At least 1	3 (1%)	4 (1%)	1 (1%)	1 (1%)	6 (1%)	1 (0%)
	Unknown	0 (0%)	1 (0%)	1 (1%)	0 (0%)	1 (0%)	0 (0%)
Sentinel Node Biopsy	Yes	127 (22%)	121 (21%)	37 (20%)	39 (21%)	146 (24%)	102 (19%)
	No	447 (78%)	452 (79%)	151 (80%)	150 (79%)	469 (76%)	430 (81%)

		Tumour bed boost		WBRT dose-fractionation (Category A)		WBRT dose-fractionation (all patients)	
		No boost (N=574)	Boost (N=573)	Conventional (N=188)	Hypofractionated (N=189)	Conventional (N=615)	Hypofractionated (N=532)
Axillary Dissection	Yes	8 (1%)	13 (2%)	0 (0%)	1 (1%)	12 (2%)	9 (2%)
	No	566 (99%)	560 (98%)	188 (100%)	188 (99%)	603 (98%)	523 (98%)
Microscopic tumour size	Less than or equal to 20mm	358 (62%)	368 (64%)	115 (61%)	117 (62%)	371 (60%)	355 (67%)
	21mm to 50mm	172 (30%)	165 (29%)	55 (29%)	63 (33%)	194 (32%)	143 (27%)
	Greater than 50mm	25 (4%)	24 (4%)	16 (9%)	8 (4%)	29 (5%)	20 (4%)
	Unknown	19 (3%)	16 (3%)	2 (1%)	1 (1%)	21 (3%)	14 (3%)
Months from surgery to randomization	Mean (s.d.)	1.4 (0.9)	1.4 (0.6)	1.5 (0.6)	1.5 (0.6)	1.4 (0.5)	1.5 (1.0)
	Min , Max	0.3 , 3.0	0.3 , 3.0	0.3 , 2.9	0.3 , 2.8	0.3 , 2.9	0.3 , 3.0
	Median (Q1 , Q3)	1.4 (1.0 , 1.8)	1.4 (1.0 , 1.8)	1.4 (1.1 , 1.9)	1.4 (1.0 , 1.8)	1.3 (1.0 , 1.7)	1.5 (1.1 , 1.9)
Planned endocrine therapy	Yes	78 (14%)	82 (14%)	17 (9%)	19 (10%)	49 (8%)	111 (21%)
	No	496 (86%)	491 (86%)	171 (91%)	170 (90%)	566 (92%)	421 9%)
Menopausal status	Premenopausal	156 (27%)	166 (29%)	53 (28%)	57 (30%)	175 (28%)	147 (28%)
	Postmenopausal	416 (72%)	406 (71%)	135 (72%)	130 (69%)	440 (72%)	382 (72%)
	Unknown	2 (0%)	1 (0%)	0 (0%)	2 (1%)	0 (0%)	3 (1%)
Initial tumour presentation	Non-palpable lesion	481 (84%)	480 (84%)	164 (87%)	165 (87%)	504 (82%)	457 (86%)
	Palpable lesion	55 (10%)	55 (10%)	19 (10%)	18 (10%)	61 (10%)	49 (9%)
	Unknown	38 (7%)	38 (7%)	5 (3%)	6 (3%)	50 (8%)	26 (5%)
Laterality of breast tumour	Left	285 (50%)	299 (52%)	87 (46%)	97 (51%)	307 (50%)	277 (52%)
	Right	289 (50%)	274 (48%)	101 (54%)	92 (49%)	308 (50%)	255 (48%)

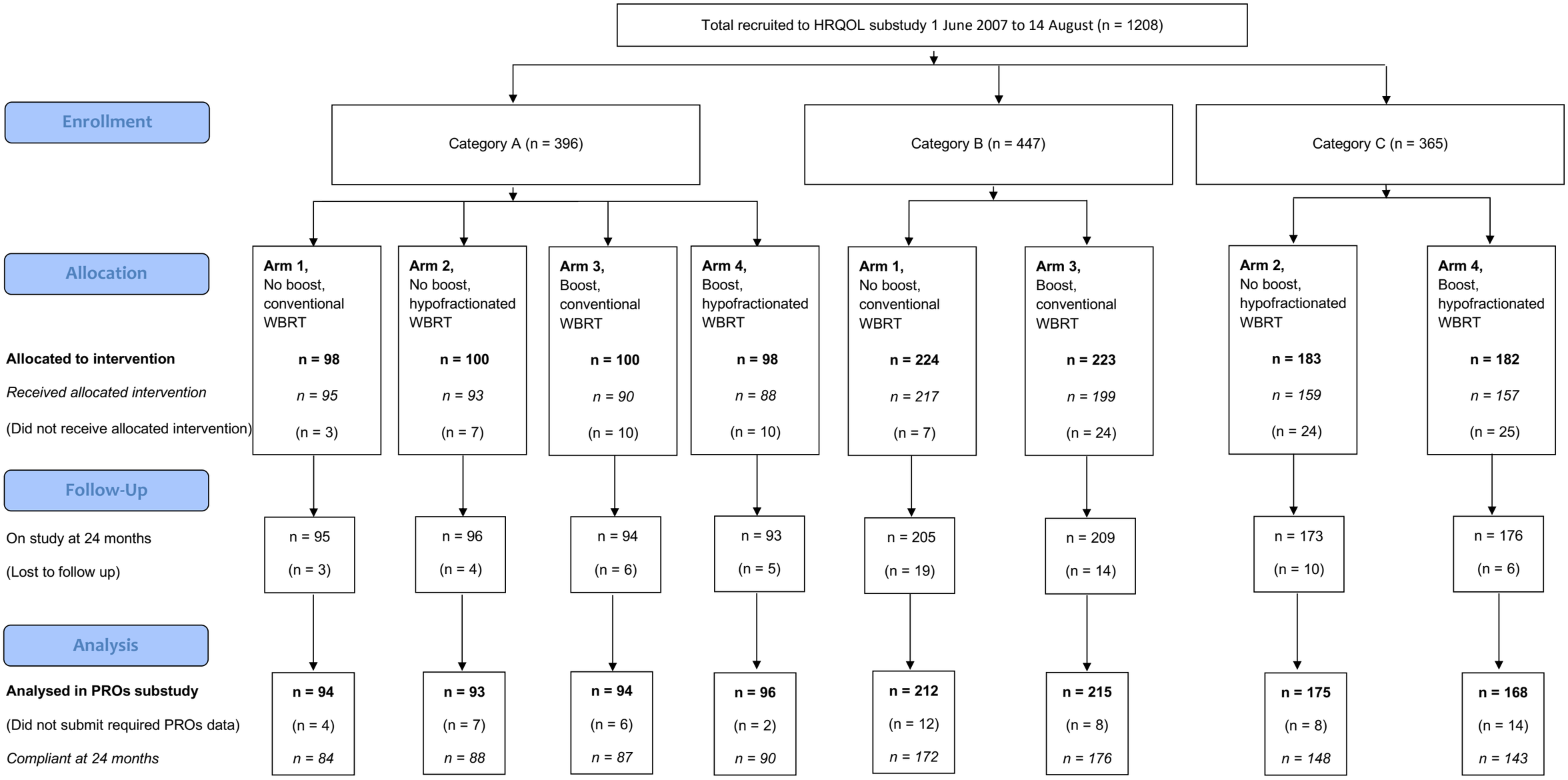
*These 1147 patients completed measures at baseline and at least one other time point.

Table 2: Compliance with the planned PRO assessment schedule for the EORTC QLQ-C30 for n=1208 patients recruited to the quality of life substudy of the BIG 3-07 trial (all sites, 1 June 2007 – 14 August 2013)

HRQOL data collection time-point	Number of patients recruited to HRQOL study and still on study[c] (N) at HRQOL data collection time-point			Compliance[a] with planned HRQOL questionnaires (n)			Percentage of patients still on study with missing HRQOL data		
	No boost	Boost	Total	No boost	Boost	Total	No boost (%)	Boost (%)	Total (%)
Baseline	605	603	1207[b]	574	573	1147	5.0 %	5.0 %	5.0 %
End of RT	598	590	1188	550	541	1091	8.0 %	8.3 %	8.2 %
6 months post RT	583	571	1154	507	512	1019	13 %	10 %	12 %
12 months post RT	582	572	1154	523	523	1046	10 %	8.6 %	9.4 %
24 months post RT	569	572	1141	492	496	988	14 %	13 %	13 %

a. Compliance with the planned PRO assessment schedule was calculated for each PRO data collection time point as the proportion of patients still on study at that time point.
b. One patient of the 1208 withdrew from HRQOL study prior to baseline as she did not speak English.
c. On study indicates the patient had not: died, withdrawn consent for further involvement in the study, or been reported as lost to follow up by the site.

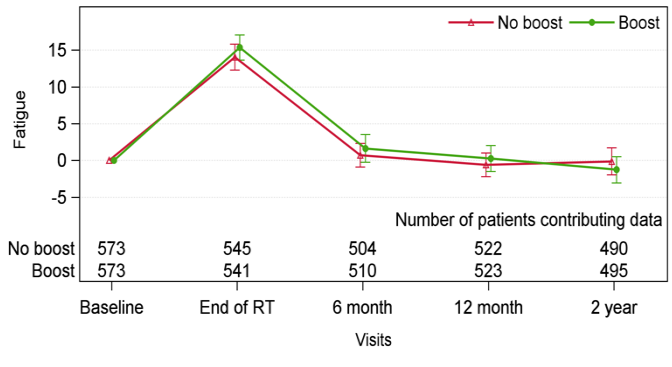
Figure 1. CONSORT diagram for BIG 3-07/TROG 07.01 quality of life substudy



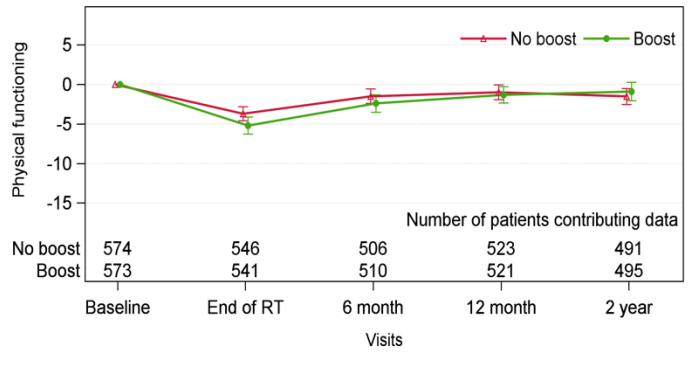
On study indicates the patient had not: died, withdrawn consent for further involvement in the study, or been reported as lost to follow up by the site.
Compliant at 24 months indicates that the patient submitted planned HRQOL questionnaires at the 24 month timepoint. “Did not receive allocated intervention” was determined as site not reporting treatment with allocated total dose and fractions for both boost or no boost and fractionation schedule.

Figure 2. Mean changes from baseline (with 95% confidence intervals) by tumour bed boost for the pre-specified key PROs.

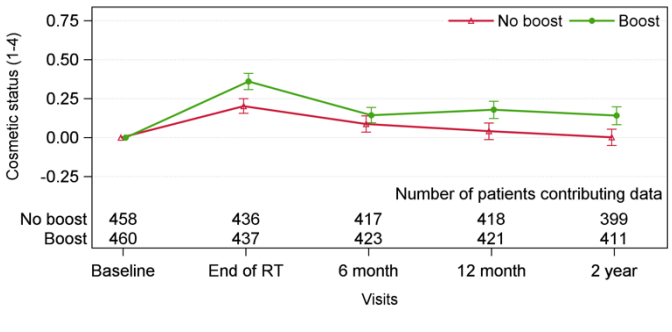
2a) EORTC QLQ-C30 Fatigue (higher is worse)



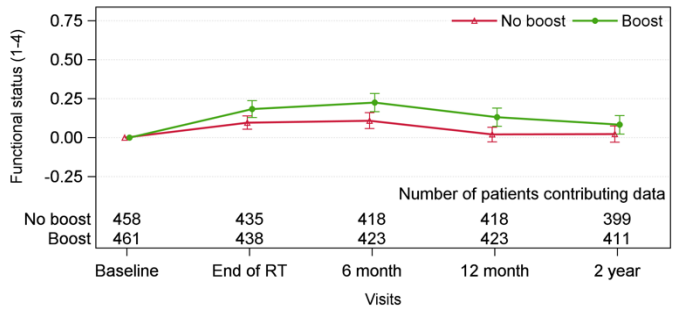
2b) EORTC QLQ-C30 Physical functioning (higher is better)



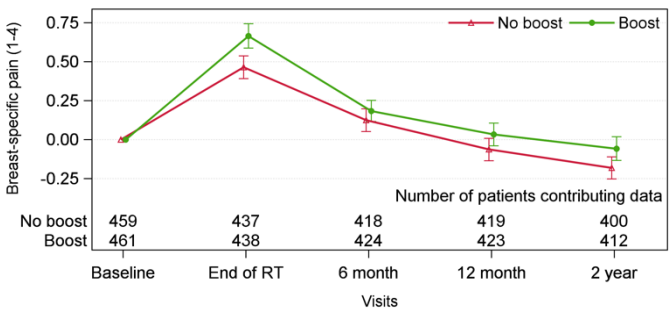
2c) BCTOS Cosmetic Status (higher is worse)



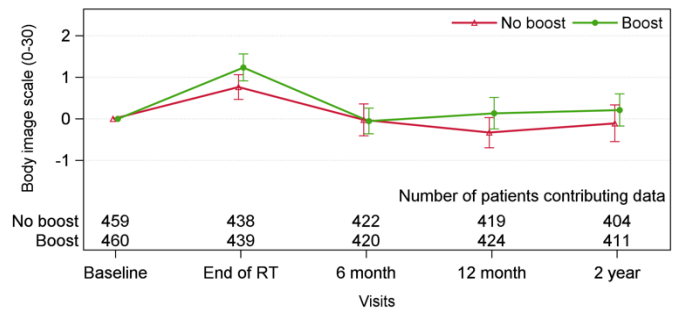
2d) BCTOS Arm and Shoulder Functional Status (higher is worse)



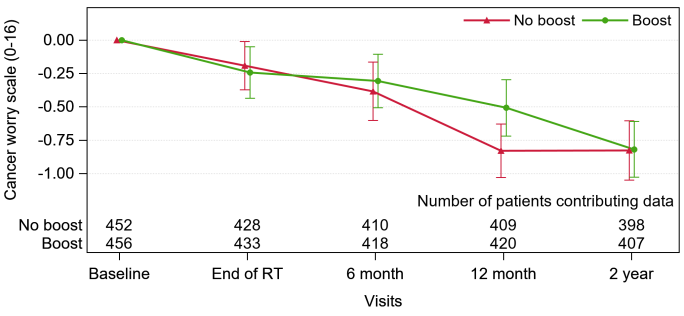
2e) BCTOS Breast Symptoms (higher is worse)



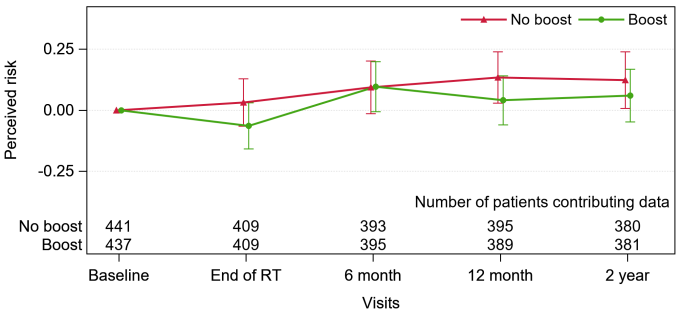
2f) Body Image Scale (BIS) (higher is worse)



2g) Cancer Worry Scale (CWS) (higher is worse)



2h) Perceived risk of invasive breast cancer (higher is worse)



EORTC QLQ-C30 scales range from 0-100. **Body Image Scale** (BIS) ranges from 0-30. **Cancer Worry Scale** (CWS) ranges 0-16.

Breast Cancer Treatment Outcome Scale (BCTOS): All scales range 1-4, higher score indicates more asymmetry between treated and untreated side. **Cosmetic status** issues include: breast size, texture, shape and elevation, nipple appearance, scar tissue, and fit of bra and clothing. **Functional status** issues include: arm and shoulder movement, stiffness and pain and ability to lift objects. **Breast-specific symptoms** include breast pain, tenderness and sensitivity.

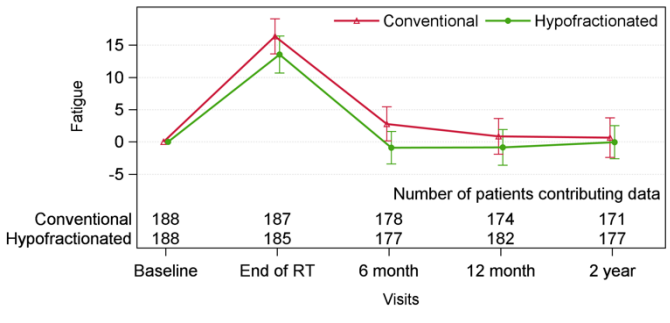
Perceived risk of invasive breast cancer: "In your opinion, compared with other women your age who have had DCIS, what are your chances of getting invasive breast cancer?", five response options: much lower (1); somewhat lower (2); the same (3); somewhat higher (4); a lot higher (5).

These plots represent mean changes and 95% confidence intervals calculated from the raw data; they are not model estimates, and they are not adjusted for any covariates.

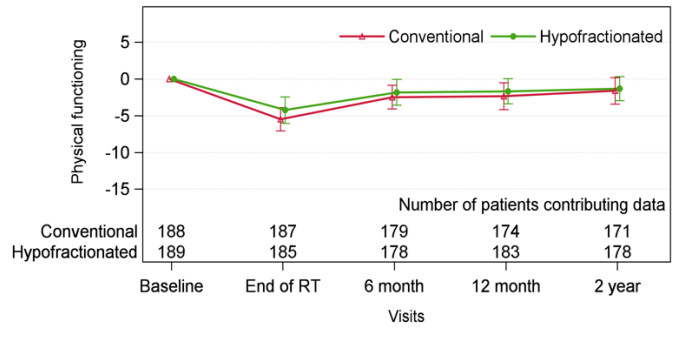
On study indicates the patient had not: died, withdrawn consent for further involvement in the study, or been reported as lost to follow up by the site.
Compliant at 24 months indicates that the patient submitted planned HRQOL questionnaires at the 24 month timepoint. "Did not receive allocated intervention" was determined as site not reporting treatment with allocated total dose and fractions for both boost or no boost and fractionation schedule.

Figure 3. Mean of changes from baseline (with 95% confidence intervals) by radiation dose fractionation (Category A patients only) for the pre-specified key PROs.

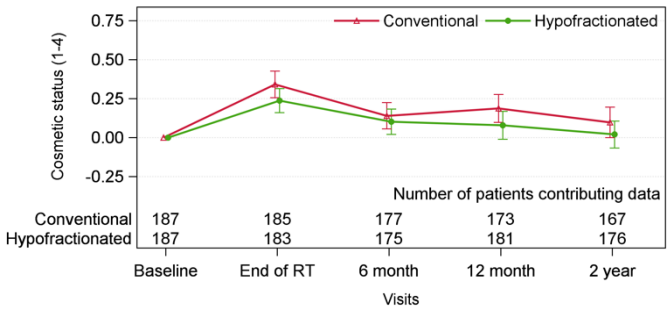
3a) QLQ-C30 Fatigue (higher is worse)



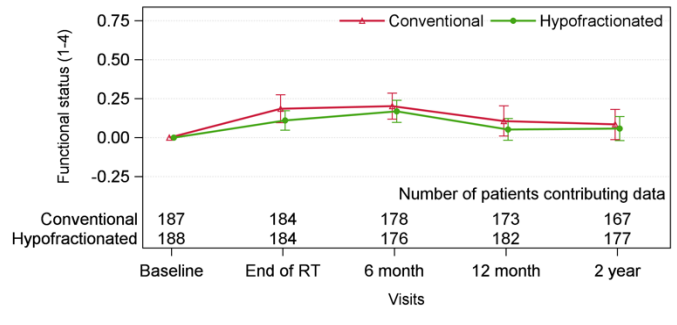
3b) QLQ-C30 Physical functioning (higher is better)



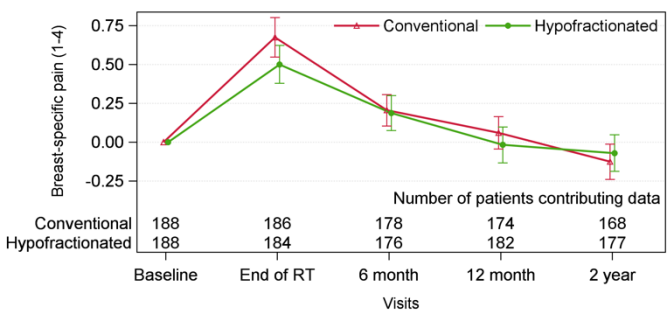
3c) BCTOS Cosmetic Status (higher is worse)



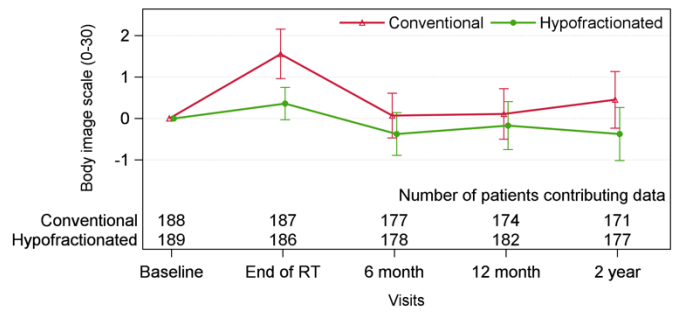
3d) BCTOS Functional Status (higher is worse)



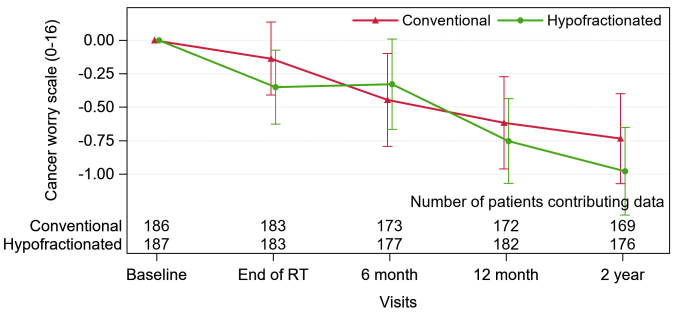
3e) BCTOS Breast Symptoms (higher is worse)



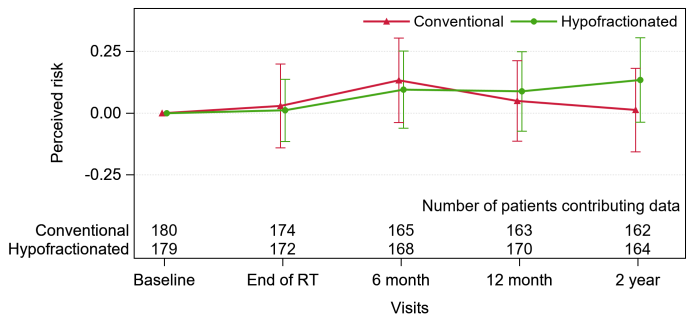
3f) Body Image Scale (BIS) (higher is worse)



3g) Cancer Worry Scale (CWS) (higher is worse)



3h) Perceived risk of invasive breast cancer (higher is worse)



EORTC QLQ-C30 scales range from 0-100. **Body Image Scale** (BIS) ranges from 0-30. **Cancer Worry Scale** (CWS) ranges 0-16.

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Quality of life after breast conserving therapy and adjuvant radiotherapy for non-low risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised controlled trial

Madeleine T. King, Emma K. Link, Tim Whelan, Ivo A. Olivotto, Ian Kunkler, A. Helen Westenberg, Guenther Gruber, Penny Schofield, Boon H. Chua on behalf of the BIG 3-07/TROG 07.01 trial investigators.

Supplementary appendix

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Figure A. Randomisation categories

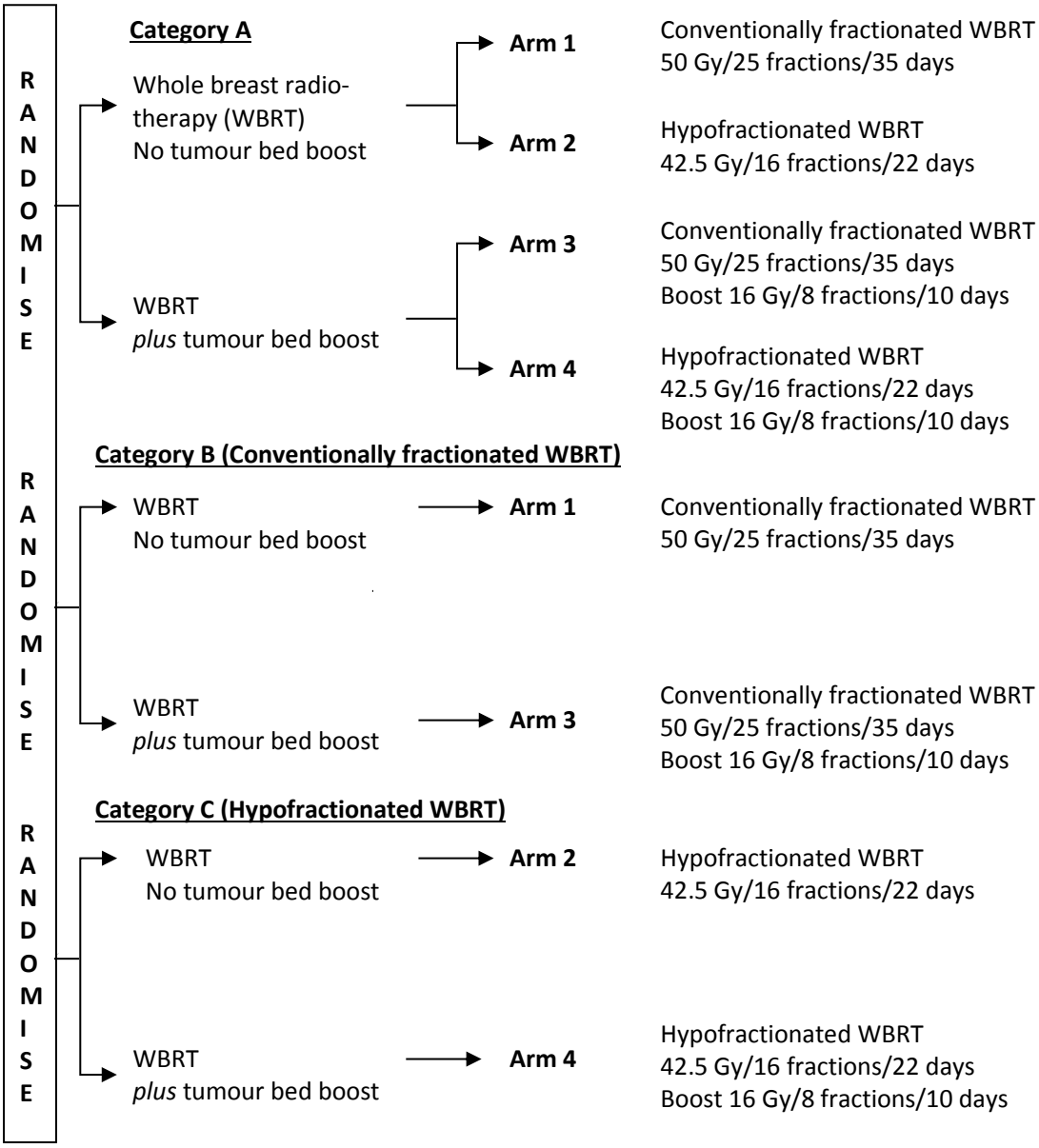
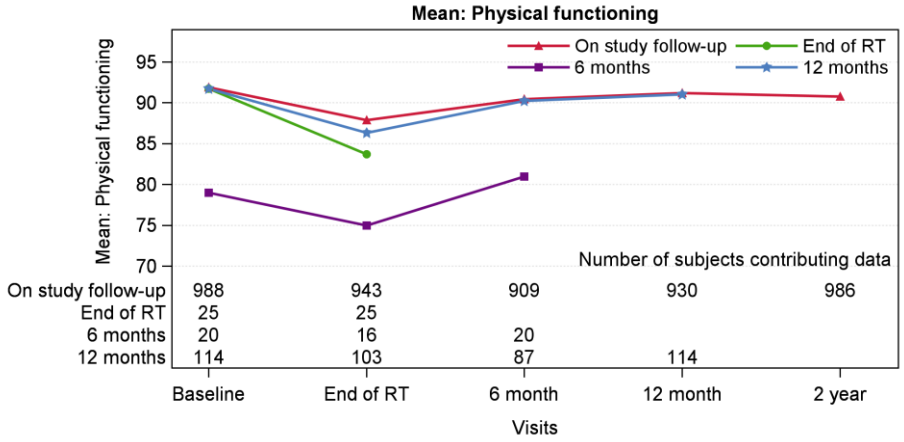
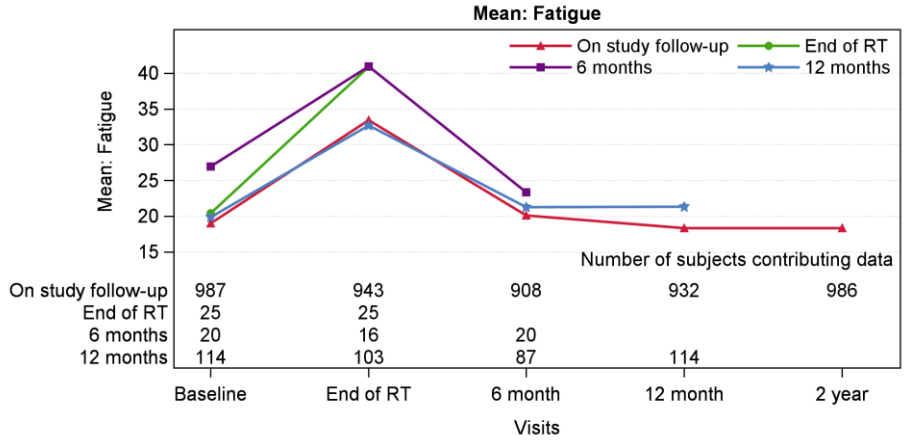


Figure B Missing data patterns for key PROs: trajectories of mean scores over time stratified by dropout time

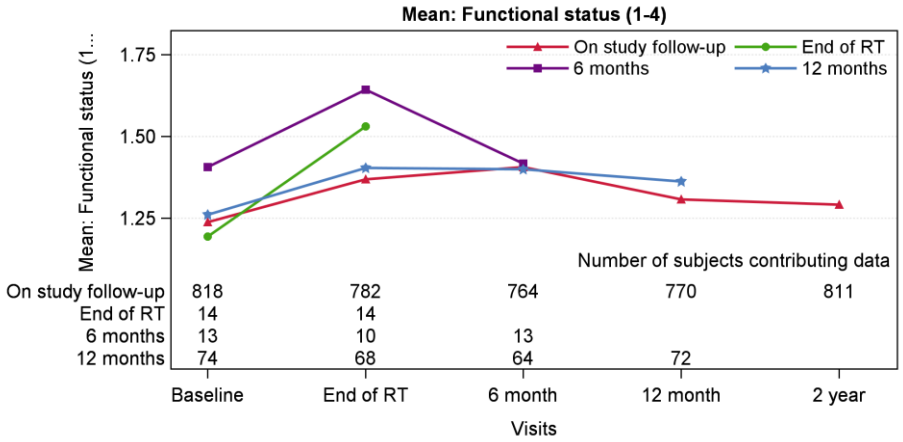
a) EORTC QLQ-C30 Physical functioning (scale range: 0-100, higher is better)



b) EORTC QLQ-C30 Fatigue (scale range: 0-100, higher is worse)



c) BCTOS Arm/Shoulder functional status (scale range: 1-4, higher is worse)



d) BCTOS Cosmetic status (scale range: 1-4, higher is worse)

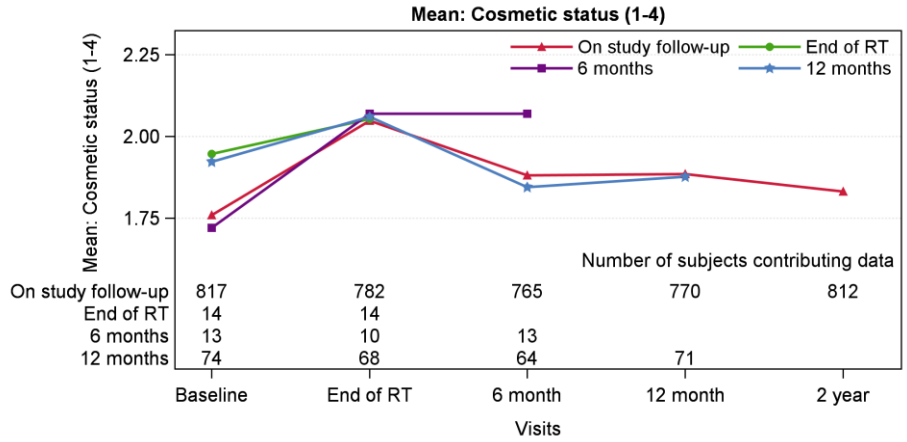
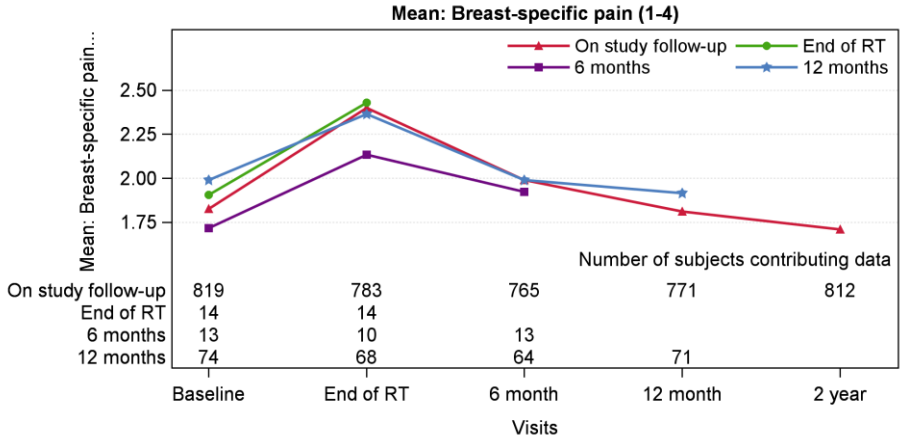
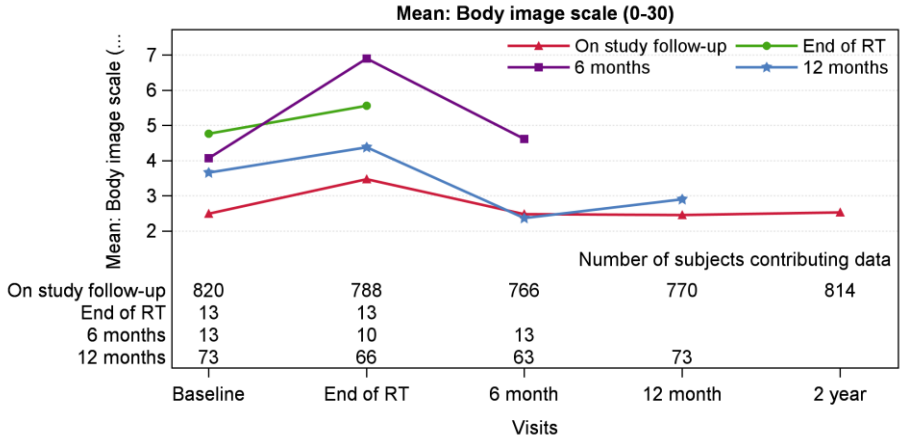


Figure B: (cont.) Missing data patterns for key PROs: trajectories of mean scores over time stratified by dropout time

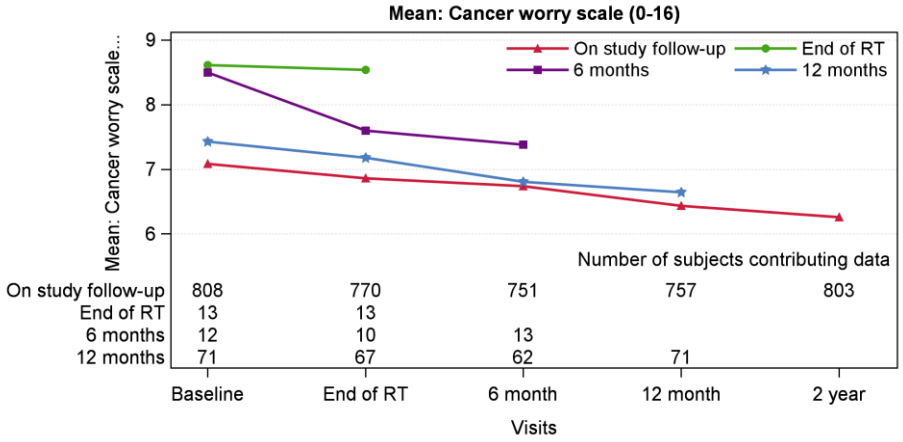
e) BCTOS breast-specific symptoms (scale range: 1-4, higher is worse)



f) Body image scale (scale range: 0-30, higher is worse)



g) Cancer worry scale (scale range: 0-16, higher is worse)



h) Perceived risk of invasive breast (5-point Likert scale, higher is worse)

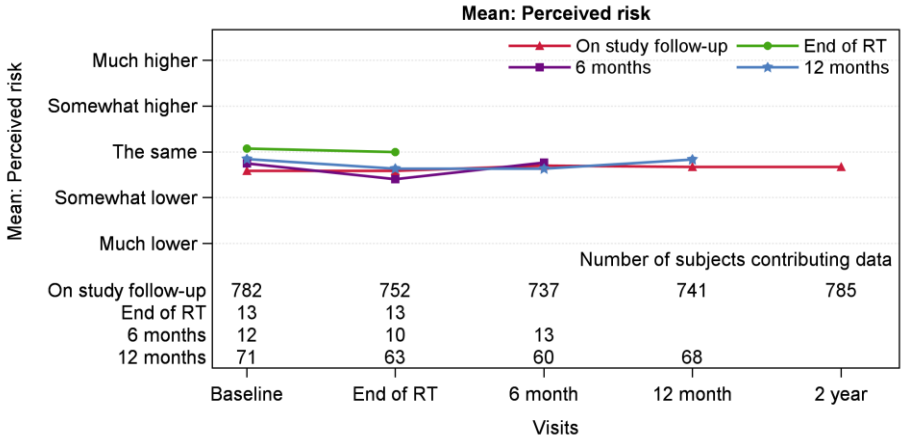
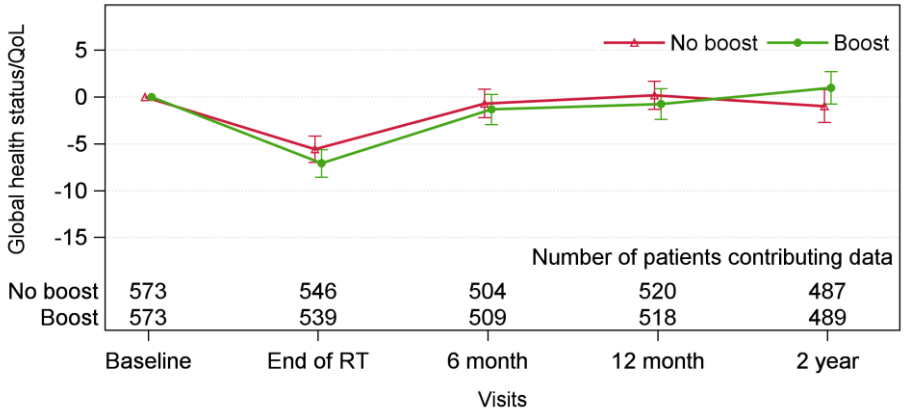
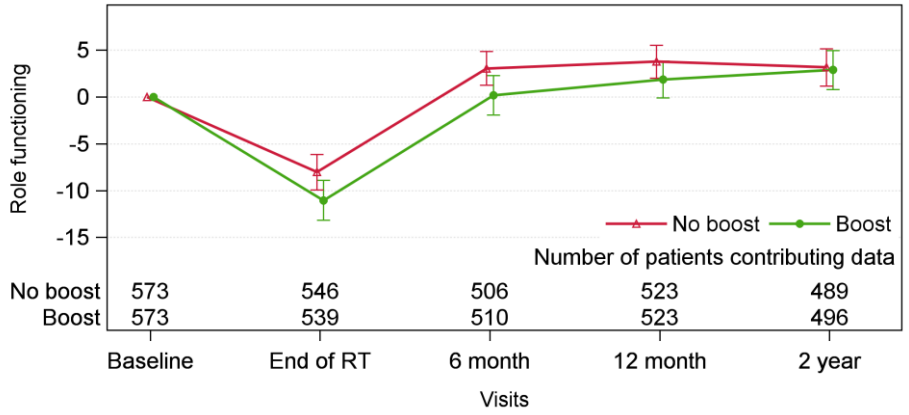


Figure C. Mean changes from baseline* (with 95% confidence intervals) by tumour bed boost for the exploratory PROs.

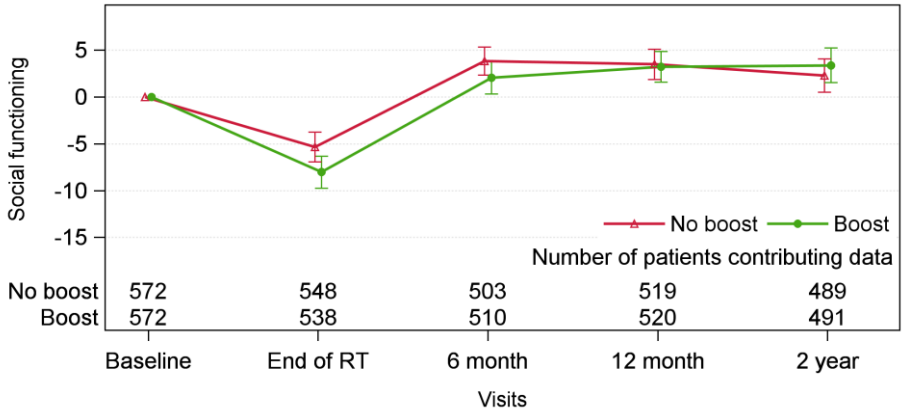
a) EORTC QLQ-C30 Global HRQL (higher is better)



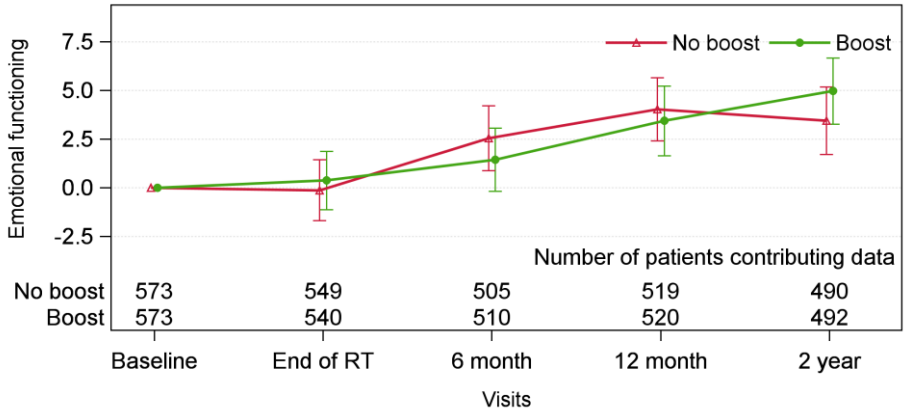
b) EORTC QLQ-C30 Role functioning (higher is better)



c) EORTC QLQ-C30 Social functioning (higher is better)



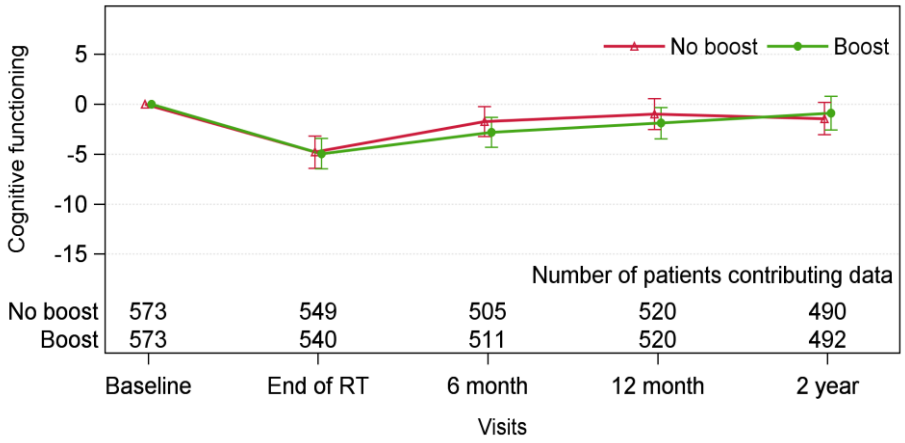
d) EORTC QLQ-C30 Emotional functioning (higher is better)



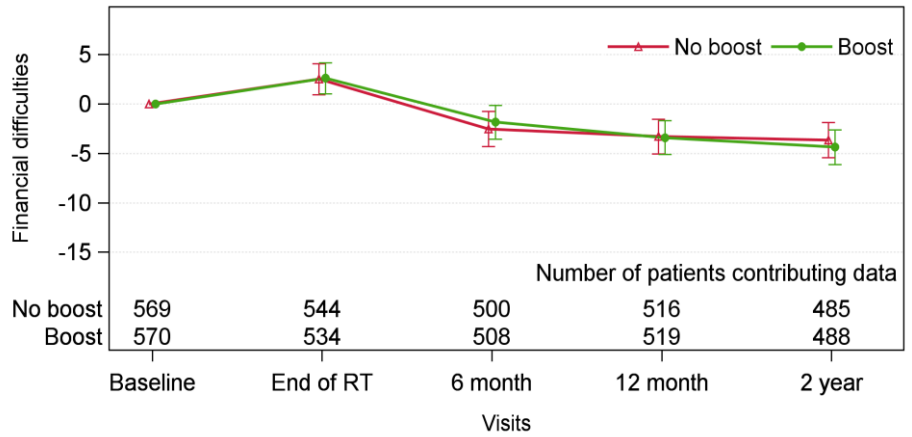
** Change from baseline calculated as follow-up value minus baseline value*

Figure C: (cont.) Mean changes from baseline* (with 95% confidence intervals) by tumour bed boost for the exploratory PROs.

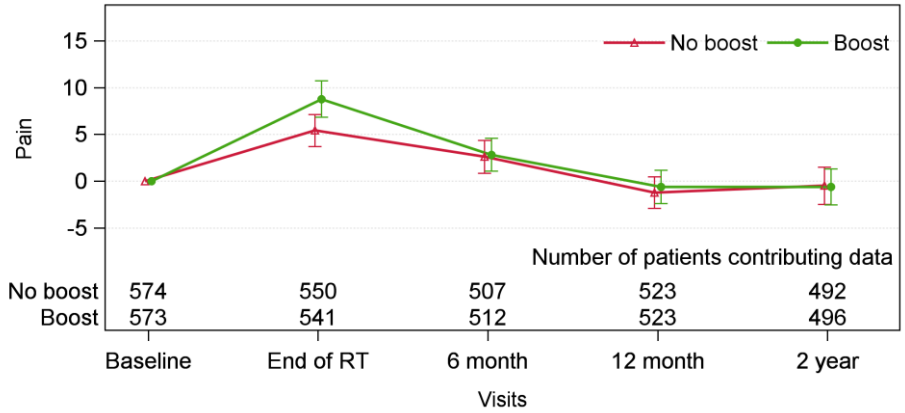
e) EORTC QLQ-C30 Cognitive (higher is better)



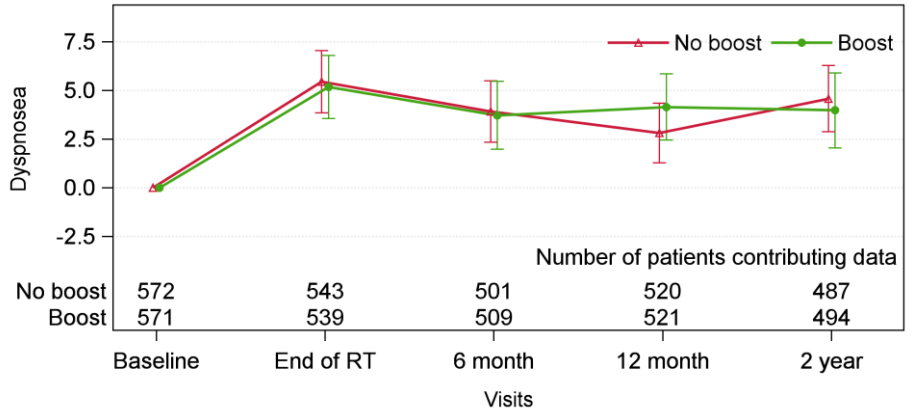
f) EORTC QLQ-C30 Financial impact (higher is worse)



g) EORTC QLQ-C30 Pain (higher is worse)



h) EORTC QLQ-C30 Dyspnoea (higher is worse)

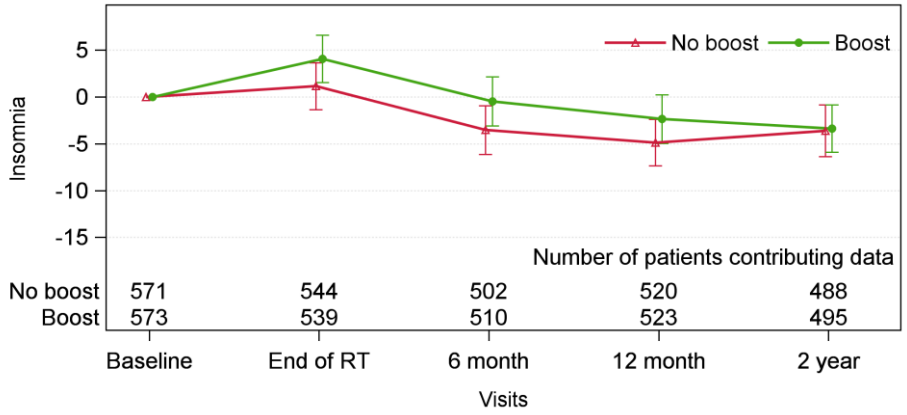


All **EORTC QLQ-C30 scales** range from 0-100.

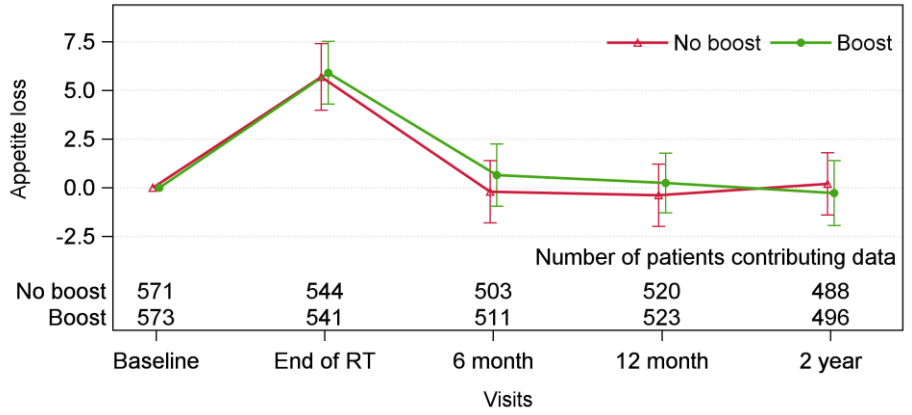
** Change from baseline calculated as follow-up value minus baseline value*

Figure C: (cont.) Mean changes from baseline* (with 95% confidence intervals) by tumour bed boost for the exploratory PROs.

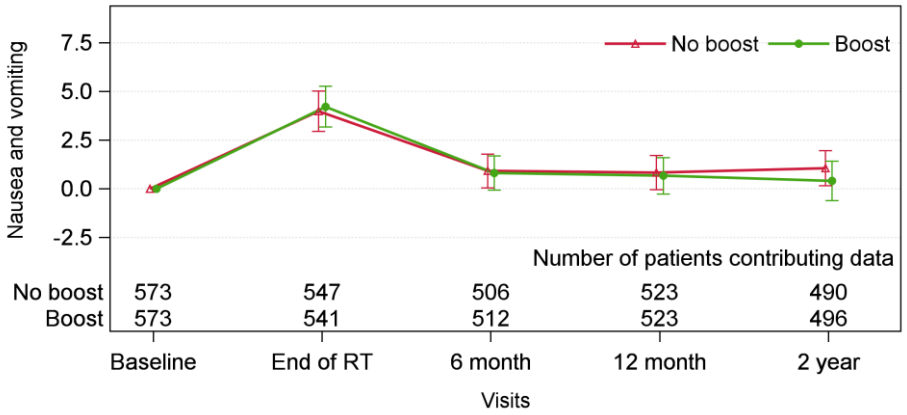
i) EORTC QLQ-C30 Insomnia (higher is worse)



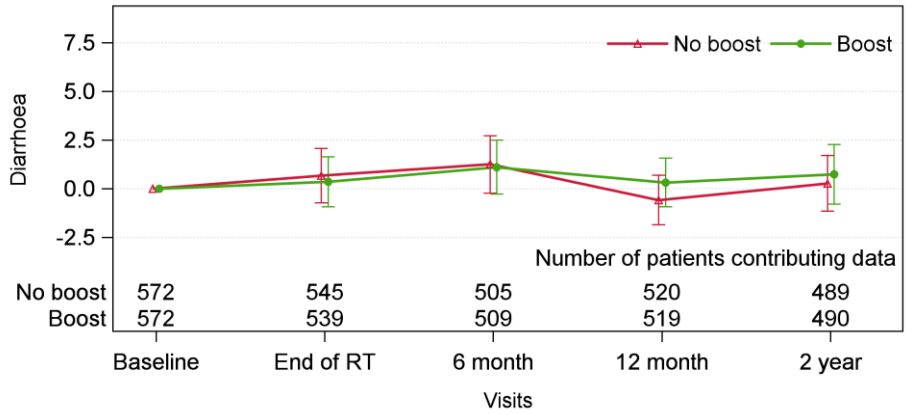
j) EORTC QLQ-C30 Loss of appetite (higher is worse)



k) EORTC QLQ-C30 Nausea/vomiting (higher is worse)



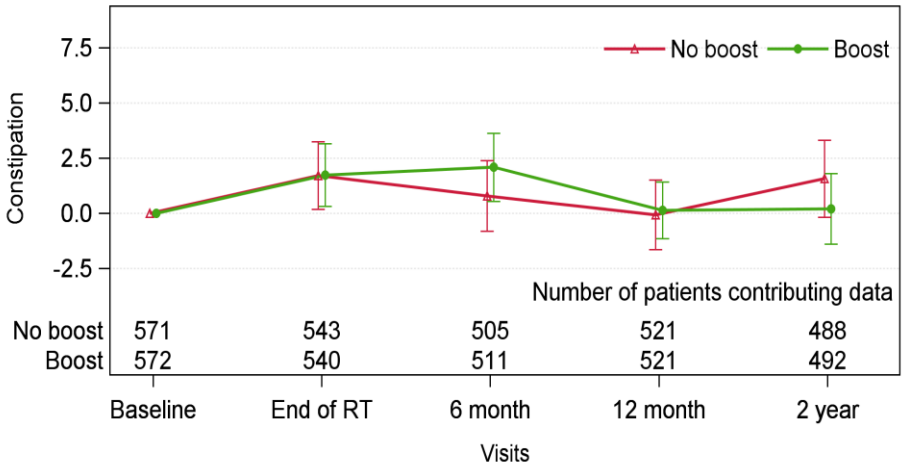
l) EORTC QLQ-C30 Diarrhoea (higher is worse)



** Change from baseline calculated as follow-up value minus baseline value*

Figure C: (cont.) Mean changes from baseline* (with 95% confidence intervals) by tumour bed boost for the exploratory PROs.

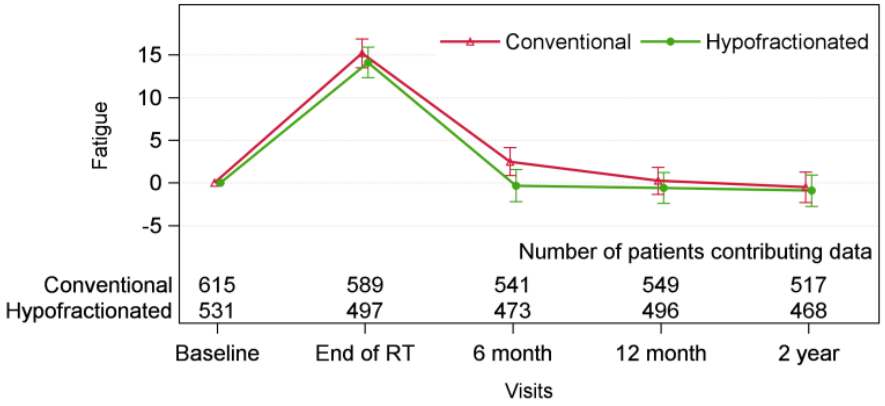
m) EORTC QLQ-C30 Constipation (higher is worse)



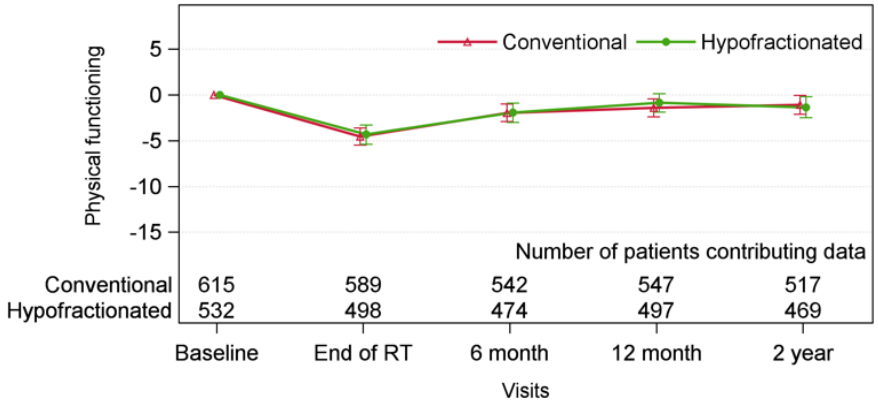
** Change from baseline calculated as follow-up value minus baseline value*

Figure D. Mean of changes from baseline* by radiation dose fractionation among all patients, for the pre-specified key PROs.

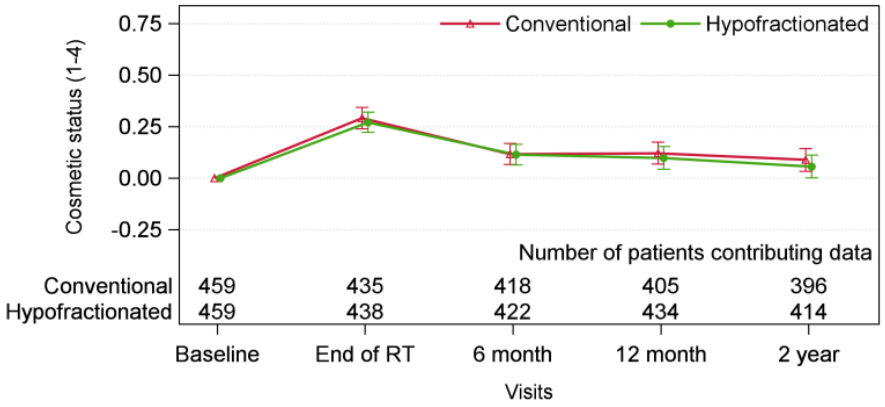
a) EORTC QLQ-C30 Fatigue (higher is worse)



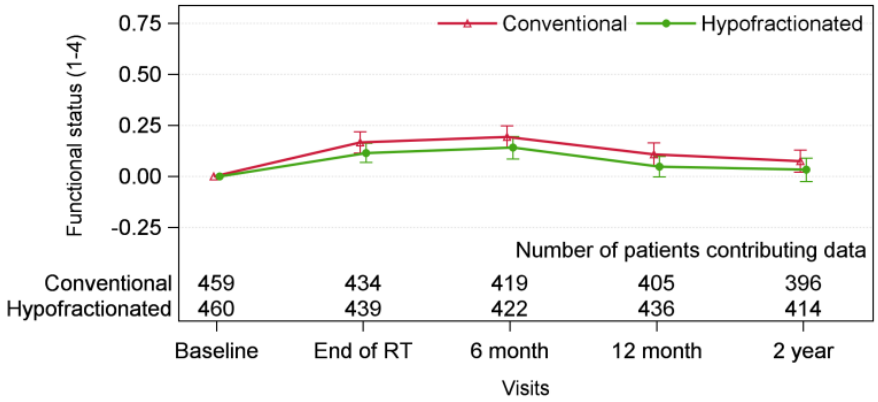
b) EORTC QLQ-C30 Physical functioning (higher is better)



c) BCTOS Cosmetic Status (higher is worse)

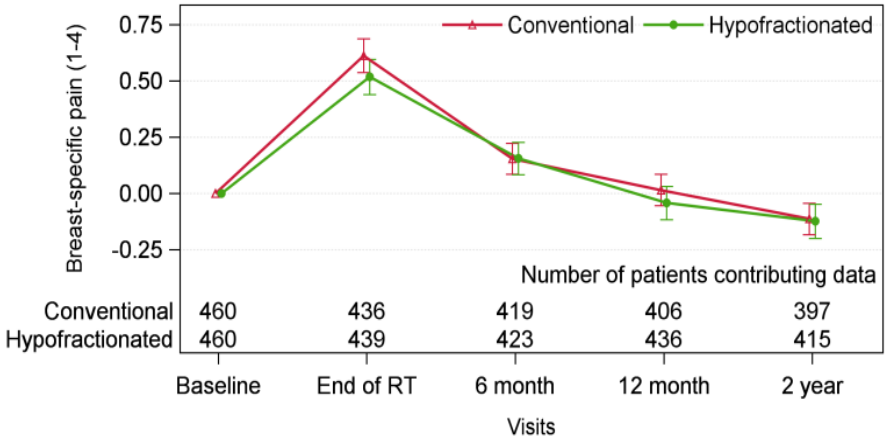


d) BCTOS Functional Status (higher is worse)

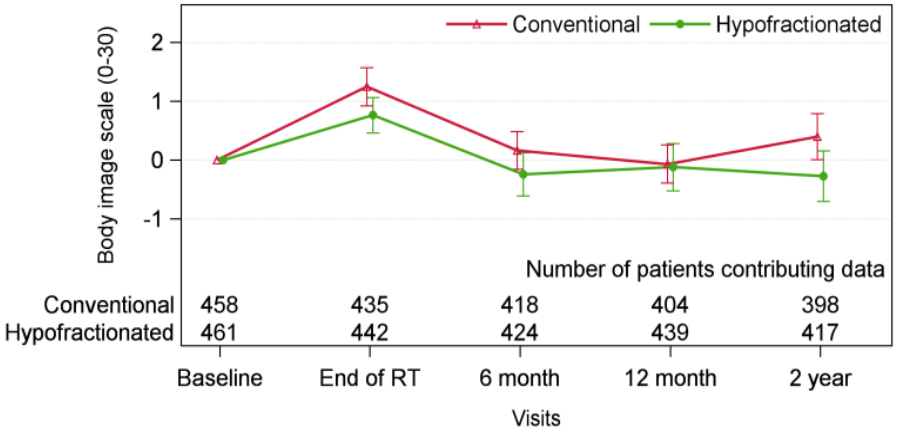


** Change from baseline calculated as follow-up value minus baseline value*

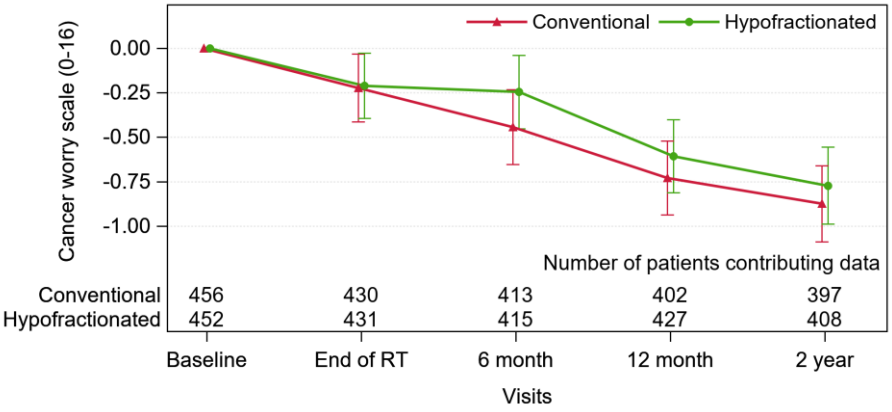
e) BCTOS Breast Symptoms (higher is worse)



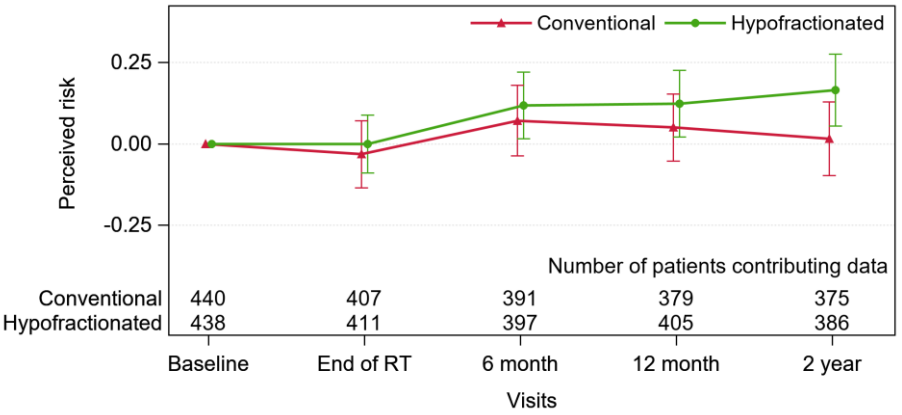
f) Body Image Scale (BIS) (higher is worse)



g) Cancer Worry Scale (CWS) (higher is worse)



h) Perceived risk of invasive breast cancer (higher is worse)



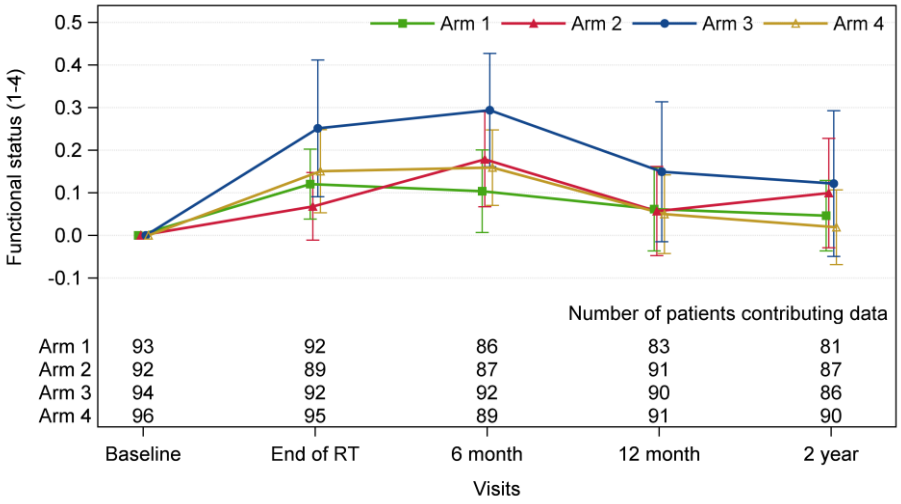
EORTC QLQ-C30 scales range from 0-100. **Body Image Scale** (BIS) ranges from 0-30. **Cancer Worry Scale** (CWS) ranges 0-16.

Breast Cancer Treatment Outcome Scale (BCTOS): All scales range 1-4, higher score indicates more asymmetry between treated and untreated side. **Cosmetic status** issues include: breast size, texture, shape and elevation, nipple appearance, scar tissue, and fit of bra and clothing. **Functional status** issues include: arm and shoulder movement, stiffness and pain and ability to lift objects. **Breast-specific symptoms** include breast pain, tenderness and sensitivity.

Perceived risk of invasive breast cancer: "In your opinion, compared with other women your age who have had DCIS, what are your chances of getting invasive breast cancer?", five response options: much lower (1); somewhat lower (2); the same (3); somewhat higher (4); a lot higher (5).

These plots represent mean changes (calculated as follow-up value minus baseline value) and 95% confidence intervals calculated from the raw data; they are not model estimates, and they are not adjusted for any covariates.

Figure E. Mean of changes from baseline in arm and shoulder-related functional status (BCTOS-FS) with 95% CI by randomised arm (positive change indicates worsening), Category A patients only: Arm 1 [conventionally fractionated whole breast radiotherapy (WBRT) only], Arm 2 [hypofractionated WBRT only], Arm 3 [conventionally fractionated WBRT + tumour bed boost (TBB)], Arm 4 [hypofractionated WBRT +TBB]



Supplementary Table A. Hospital anxiety and depression scale and distress summaries over time by tumour bed boost

A higher scale indicates more anxiety/depression or distress.

		No boost					Boost				
		Baseline (N=88)	**End of RT (N=88)**	**6 month (N=86)**	**12 month (N=82)**	**2 year (N=81)**	**Baseline (N=86)**	**End of RT (N=83)**	**6 month (N=81)**	**12 month (N=80)**	**2 year (N=82)**
Hospital anxiety scale (0-21)	N	88	86	57	41	10	86	82	54	38	13
	Mean (s.d.)	8.17 (1.16)	8.28 (1.83)	8.16 (1.42)	8.37 (1.11)	7.90 (1.37)	8.02 (1.61)	7.80 (1.20)	7.89 (1.27)	7.97 (1.33)	8.62 (1.45)
Hospital depression scale (0-21)	N	87	87	57	41	10	84	82	54	38	13
	Mean (s.d.)	12.46 (2.41)	12.28 (2.64)	12.39 (2.80)	12.78 (2.57)	12.90 (2.92)	12.60 (2.30)	12.96 (1.82)	12.46 (2.40)	12.47 (2.60)	12.77 (2.42)
Distress thermometer (0-10)	N	84	83	54	39	10	83	80	49	38	12
	Mean (s.d.)	2.62 (2.41)	2.48 (2.24)	2.41 (2.59)	1.72 (2.10)	2.10 (3.18)	2.63 (2.34)	2.59 (2.44)	2.69 (2.80)	3.26 (2.85)	2.42 (2.23)

Supplementary Table B. Patient-reported outcome summaries over time by tumour bed boost

Tabulated form of figures: sample size, mean and standard deviation for each PROs at each assessment time point, e.g. for future use in meta-analyses.

EORTC QLQ-C30: A high score for the global health status/QoL and functional scales represent a high/healthy level of functions, but a high score for a symptom scale/item represents a high level of symptomatology/problems.
BCTOS: A higher score indicates greater perceived difference between the treated and untreated breast and area.
BIS: A higher score represents more symptoms/distress.
CWS: A higher cancer worry scale indicates more cancer worries.
Perceived risk: In your opinion, compared with other women your age who have DCIS, what are your chances of getting invasive breast cancer?

		No boost					Boost				
		Baseline (N=574)	**End of RT (N=558)**	**6 month (N=526)**	**12 month (N=538)**	**2 year (N=505)**	**Baseline (N=573)**	**End of RT (N=560)**	**6 month (N=533)**	**12 month (N=534)**	**2 year (N=513)**
EORTC QLQ-C30											
Global health status/QoL	N	573	547	505	521	487	573	539	509	518	489
	Mean (s.d.)	78.1 (17.3)	72.8 (19.4)	78.2 (18.0)	78.9 (18.3)	77.8 (20.1)	78.6 (17.4)	72.0 (18.8)	77.6 (18.3)	78.4 (17.9)	79.9 (17.8)
Physical functioning	N	574	546	506	523	491	573	541	510	521	495
	Mean (s.d.)	91.8 (11.2)	88.3 (13.6)	90.9 (12.1)	91.4 (12.8)	90.5 (13.5)	91.5 (12.9)	86.6 (15.3)	89.6 (14.6)	91.0 (13.3)	91.1 (13.7)
Role functioning	N	573	547	506	523	490	573	539	510	523	496
	Mean (s.d.)	88.3 (19.0)	80.3 (23.3)	91.9 (16.3)	92.1 (16.3)	91.4 (19.0)	87.5 (20.2)	76.6 (24.8)	88.1 (20.7)	90.1 (19.8)	90.7 (19.6)
Emotional functioning	N	573	550	506	520	490	573	540	510	520	492
	Mean (s.d.)	79.0 (19.5)	79.2 (20.6)	82.2 (19.6)	83.2 (19.3)	83.5 (19.0)	79.2 (18.9)	79.8 (19.3)	81.1 (19.0)	83.1 (19.7)	84.3 (18.7)
Cognitive functioning	N	573	550	506	521	490	573	540	511	520	492
	Mean (s.d.)	87.6 (17.2)	83.1 (20.3)	86.6 (17.6)	87.0 (18.0)	86.9 (18.1)	88.0 (17.5)	83.0 (20.5)	85.8 (17.6)	86.4 (17.6)	87.2 (18.6)
Social functioning	N	572	550	505	521	490	572	539	510	520	492
	Mean (s.d.)	90.1 (17.2)	84.7 (20.5)	94.3 (13.1)	93.8 (15.5)	92.9 (18.1)	89.4 (17.1)	81.4 (22.2)	91.4 (16.8)	93.0 (15.4)	93.0 (16.9)
Fatigue	N	573	546	505	523	491	573	541	510	523	495
	Mean (s.d.)	19.0 (18.2)	32.7 (23.0)	19.1 (18.8)	17.9 (19.0)	18.5 (20.6)	19.6 (19.0)	34.7 (22.1)	21.5 (20.6)	19.5 (19.7)	18.2 (19.9)
Nausea/vomiting	N	573	548	506	523	491	573	541	512	523	496

		No boost					Boost				
		Baseline (N=574)	**End of RT (N=558)**	**6 month (N=526)**	**12 month (N=538)**	**2 year (N=505)**	**Baseline (N=573)**	**End of RT (N=560)**	**6 month (N=533)**	**12 month (N=534)**	**2 year (N=513)**
	Mean (s.d.)	2.3 (8.2)	6.2 (12.7)	3.0 (9.1)	3.0 (9.2)	3.0 (9.5)	2.5 (8.1)	6.7 (12.6)	3.3 (9.4)	3.1 (10.4)	2.8 (10.4)
Pain	N	574	550	507	523	492	573	541	512	523	496
	Mean (s.d.)	14.6 (18.4)	19.8 (20.3)	16.8 (20.2)	12.8 (19.7)	14.1 (21.8)	14.3 (19.4)	22.9 (22.5)	17.2 (21.1)	13.2 (19.2)	13.0 (19.9)
Dyspnoea	N	572	545	503	522	489	571	541	511	523	496
	Mean (s.d.)	7.5 (16.8)	12.5 (21.2)	10.9 (19.1)	10.0 (18.6)	11.9 (20.8)	6.9 (16.5)	12.0 (20.4)	10.8 (20.5)	10.8 (20.4)	10.9 (21.2)
Insomnia	N	571	547	505	523	491	573	539	510	523	495
	Mean (s.d.)	28.1 (28.9)	28.6 (29.3)	24.2 (27.9)	23.5 (28.1)	23.7 (29.0)	27.1 (29.6)	31.2 (30.3)	26.6 (28.3)	24.6 (28.0)	23.8 (27.5)
Appetite loss	N	571	547	506	523	491	573	541	511	523	496
	Mean (s.d.)	6.2 (15.7)	12.0 (21.5)	6.1 (16.2)	5.5 (15.6)	6.1 (16.5)	5.1 (13.8)	11.0 (20.7)	5.5 (16.1)	5.0 (14.6)	4.4 (15.2)
Constipation	N	571	546	506	522	489	572	541	512	522	493
	Mean (s.d.)	7.5 (18.2)	9.3 (19.7)	7.8 (17.9)	7.4 (18.0)	8.9 (19.0)	6.6 (16.5)	8.4 (19.7)	9.0 (20.2)	6.7 (16.4)	6.9 (17.2)
Diarrhoea	N	572	547	506	521	489	572	540	510	520	491
	Mean (s.d.)	5.0 (14.3)	5.5 (15.3)	6.0 (15.5)	4.4 (13.5)	5.0 (14.8)	3.9 (12.4)	4.2 (12.0)	4.9 (15.1)	4.2 (13.6)	4.7 (15.3)
Financial problems	N	569	549	503	521	489	570	536	508	519	489
	Mean (s.d.)	8.8 (21.3)	11.2 (23.2)	6.0 (16.6)	5.2 (16.9)	4.2 (14.3)	9.3 (20.2)	11.7 (22.5)	7.6 (19.3)	5.5 (16.4)	4.7 (15.5)
BCTOS											
Functional status (1-4)	N	458	436	418	419	400	461	438	423	423	411
	Mean (s.d.)	1.26 (0.48)	1.34 (0.55)	1.36 (0.57)	1.27 (0.52)	1.28 (0.52)	1.23 (0.43)	1.41 (0.61)	1.45 (0.63)	1.35 (0.58)	1.30 (0.57)
Cosmetic status (1-4)	N	458	437	418	419	400	460	437	424	422	412
	Mean (s.d.)	1.80 (0.59)	1.99 (0.65)	1.89 (0.59)	1.84 (0.58)	1.78 (0.58)	1.75 (0.51)	2.11 (0.61)	1.88 (0.55)	1.93 (0.62)	1.88 (0.58)
Breast-specific symptoms (1-4)	N	459	437	418	419	400	461	438	424	423	412
	Mean (s.d.)	1.88 (0.71)	2.33 (0.78)	1.99 (0.75)	1.80 (0.70)	1.68 (0.69)	1.80 (0.62)	2.46 (0.81)	1.99 (0.71)	1.84 (0.69)	1.74 (0.69)

		No boost					Boost				
		Baseline (N=574)	**End of RT (N=558)**	**6 month (N=526)**	**12 month (N=538)**	**2 year (N=505)**	**Baseline (N=573)**	**End of RT (N=560)**	**6 month (N=533)**	**12 month (N=534)**	**2 year (N=513)**
Body image scale **(0-30)**	N	459	438	422	419	404	460	439	420	424	410
	Mean (s.d.)	2.98 (4.99)	3.69 (5.54)	2.74 (4.52)	2.56 (4.71)	2.68 (4.87)	2.31 (3.81)	3.54 (4.74)	2.26 (3.70)	2.44 (4.25)	2.44 (4.40)
Cancer worry scale **(0-16)**	N	449	428	410	408	397	455	432	416	420	406
	Mean (s.d.)	7.24 (2.57)	7.01 (2.57)	6.78 (2.27)	6.36 (2.06)	6.28 (2.16)	7.02 (2.36)	6.79 (2.22)	6.70 (2.24)	6.51 (2.32)	6.20 (2.01)
Perceived risk **(5 categories)**	N	441	418	401	403	389	437	420	409	406	396
	Much lower	83 (19%)	77 (18%)	68 (17%)	63 (16%)	63 (16%)	89 (20%)	94 (22%)	70 (17%)	81 (20%)	75 (19%)
	Somewhat lower	77 (17%)	69 (17%)	57 (14%)	68 (17%)	63 (16%)	80 (18%)	76 (18%)	76 (19%)	65 (16%)	64 (16%)
	The same	207 (47%)	201 (48%)	205 (51%)	190 (47%)	194 (50%)	200 (46%)	192 (46%)	189 (46%)	201 (50%)	202 (51%)
	Somewhat higher	61 (14%)	59 (14%)	59 (15%)	63 (16%)	57 (15%)	60 (14%)	52 (12%)	65 (16%)	54 (13%)	48 (12%)
	Much higher	13 (3%)	12 (3%)	12 (3%)	19 (5%)	12 (3%)	8 (2%)	6 (1%)	9 (2%)	5 (1%)	7 (2%)

Supplementary Table Error! No text of specified style in document.**C1.** Patient characteristics at baseline for patients included in PRO analysis by Treatment Arm, randomisation category A only (n=377): Arm 1 [conventionally fractionated whole breast radiotherapy (WBRT) only], Arm 2 [hypofractionated WBRT only], Arm 3 [conventionally fractionated WBRT + tumour bed boost (TBB)], Arm 4 [hypofractionated WBRT +TBB]

			Treatment arm			
		Total (N=377)	**Arm 1 (N=94)**	**Arm 2 (N=93)**	**Arm 3 (N=94)**	**Arm 4 (N=96)**
Age	<50	73 (19%)	18 (19%)	18 (19%)	19 (20%)	18 (19%)
	≥50	304 (81%)	76 (81%)	75 (81%)	75 (80%)	78 (81%)
Region	Australia, New Zealand, Singapore	268 (71%)	67 (71%)	66 (71%)	67 (71%)	68 (71%)
	Canada	30 (8%)	7 (7%)	6 (6%)	10 (11%)	7 (7%)
	UK, Ireland	69 (18%)	17 (18%)	18 (19%)	15 (16%)	19 (20%)
	Europe	10 (3%)	3 (3%)	3 (3%)	2 (2%)	2 (2%)
Tumour Location	Upper outer quadrant	141 (37%)	32 (34%)	28 (30%)	39 (41%)	42 (44%)
	Upper inner quadrant	39 (10%)	11 (12%)	10 (11%)	11 (12%)	7 (7%)
	3 o'clock	20 (5%)	4 (4%)	4 (4%)	9 (10%)	3 (3%)
	12 o'clock	37 (10%)	9 (10%)	10 (11%)	5 (5%)	13 (14%)
	Central (within 3 cm radius of nipple)	38 (10%)	11 (12%)	10 (11%)	7 (7%)	10 (10%)
	Lower inner quadrant	24 (6%)	4 (4%)	3 (3%)	9 (10%)	8 (8%)
	Lower outer quadrant	31 (8%)	9 (10%)	13 (14%)	4 (4%)	5 (5%)
	6 o'clock	19 (5%)	6 (6%)	4 (4%)	3 (3%)	6 (6%)
	9 o'clock	28 (7%)	8 (9%)	11 (12%)	7 (7%)	2 (2%)
Number of re-excisions following initial surgery	0	234 (62%)	62 (66%)	56 (60%)	60 (64%)	56 (58%)
	1	131 (35%)	28 (30%)	35 (38%)	30 (32%)	38 (40%)
	2	8 (2%)	4 (4%)	0 (0%)	2 (2%)	2 (2%)
	3	1 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
	At least 1	2 (1%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
	Unknown	1 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Sentinel Node Biopsy	Yes	76 (20%)	18 (19%)	17 (18%)	19 (20%)	22 (23%)
	No	301 (80%)	76 (81%)	76 (82%)	75 (80%)	74 (77%)
Axillary Dissection	Yes	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
	No	376 (100%)	94 (100%)	93 (100%)	94 (100%)	95 (99%)
Microscopic Tumour size	less than or equal to 20mm	232 (62%)	56 (60%)	59 (63%)	59 (63%)	58 (60%)
	21mm to 50mm	118 (31%)	27 (29%)	27 (29%)	28 (30%)	36 (38%)

		Total (N=377)	Treatment arm Arm 1 (N=94)	Arm 2 (N=93)	Arm 3 (N=94)	Arm 4 (N=96)
	Greater than 50mm	24 (6%)	10 (11%)	6 (6%)	6 (6%)	2 (2%)
	Unknown	3 (1%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)
Months from surgery to randomisation	Mean (s.d.)	1.5 (0.6)	1.5 (0.6)	1.4 (0.6)	1.5 (0.6)	1.5 (0.6)
	Min , Max	0.3 , 2.9	0.3 , 2.6	0.3 , 2.6	0.5 , 2.9	0.4 , 2.8
	Median (Q1 , Q3)	1.4 (1.0 , 1.8)	1.4 (1.1 , 1.9)	1.5 (1.0 , 1.8)	1.4 (1.0 , 1.8)	1.4 (1.1 , 1.8)
Planned endocrine therapy	Yes	36 (10%)	8 (9%)	9 (10%)	9 (10%)	10 (10%)
	No	341 (90%)	86 (91%)	84 (90%)	85 (90%)	86 (90%)

Supplementary Table Error! No text of specified style in document.**D2.** Patient characteristics at baseline for patients included in analysis by treatment arm (n=1147): Arm 1 [conventionally fractionated whole breast radiotherapy (WBRT) only], Arm 2 [hypofractionated WBRT only], Arm 3 [conventionally fractionated WBRT + tumour bed boost (TBB)], Arm 4 [hypofractionated WBRT +TBB]

			Treatment arm			
		Total (N=1147)	**Arm 1 (N=306)**	**Arm 2 (N=268)**	**Arm 3 (N=309)**	**Arm 4 (N=264)**
Age	<50	207 (18%)	58 (19%)	44 (16%)	62 (20%)	43 (16%)
	≥50	940 (82%)	248 (81%)	224 (84%)	247 (80%)	221 (84%)
Region	Australia, New Zealand, Singapore	427 (37%)	142 (46%)	70 (26%)	143 (46%)	72 (27%)
	Canada	233 (20%)	24 (8%)	93 (35%)	27 (9%)	89 (34%)
	UK, Ireland	220 (19%)	45 (15%)	65 (24%)	45 (15%)	65 (25%)
	Europe	267 (23%)	95 (31%)	40 (15%)	94 (30%)	38 (14%)
Tumour Location	Upper outer quadrant	420 (37%)	107 (35%)	94 (35%)	117 (38%)	102 (39%)
	Upper inner quadrant	112 (10%)	32 (10%)	28 (10%)	25 (8%)	27 (10%)
	3 o'clock	77 (7%)	18 (6%)	14 (5%)	25 (8%)	20 (8%)
	12 o'clock	89 (8%)	27 (9%)	23 (9%)	19 (6%)	20 (8%)
	Central (within 3 cm radius of nipple)	156 (14%)	36 (12%)	29 (11%)	54 (17%)	37 (14%)
	Lower inner quadrant	67 (6%)	14 (5%)	21 (8%)	16 (5%)	16 (6%)
	Lower outer quadrant	100 (9%)	35 (11%)	27 (10%)	22 (7%)	16 (6%)
	6 o'clock	51 (4%)	14 (5%)	13 (5%)	9 (3%)	15 (6%)
	9 o'clock	74 (6%)	22 (7%)	19 (7%)	22 (7%)	11 (4%)
Number of re-excisions following initial surgery	0	777 (68%)	210 (69%)	185 (69%)	204 (66%)	178 (67%)
	1	336 (29%)	88 (29%)	78 (29%)	89 (29%)	81 (31%)
	2	23 (2%)	5 (2%)	2 (1%)	11 (4%)	5 (2%)
	3	3 (0%)	1 (0%)	2 (1%)	0 (0%)	0 (0%)
	At least 1	7 (1%)	2 (1%)	1 (0%)	4 (1%)	0 (0%)
	Unknown	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Sentinel Node Biopsy	Yes	248 (22%)	80 (26%)	47 (18%)	66 (21%)	55 (21%)
	No	899 (78%)	226 (74%)	221 (82%)	243 (79%)	209 (79%)
Axillary Dissection	Yes	21 (2%)	8 (3%)	0 (0%)	4 (1%)	9 (3%)
	No	1,126 (98%)	298 (97%)	268 (100%)	305 (99%)	255 (97%)
Microscopic Tumour size	less than or equal to 20mm	726 (63%)	177 (58%)	181 (68%)	194 (63%)	174 (66%)
	21mm to 50mm	337 (29%)	103 (34%)	69 (26%)	91 (29%)	74 (28%)
	Greater than 50mm	49 (4%)	15 (5%)	10 (4%)	14 (5%)	10 (4%)

		Total (N=1147)	Treatment arm Arm 1 (N=306)	Arm 2 (N=268)	Arm 3 (N=309)	Arm 4 (N=264)
	Unknown	35 (3%)	11 (4%)	8 (3%)	10 (3%)	6 (2%)
Months from surgery to randomisation	Mean (s.d.)	1.4 (0.8)	1.4 (0.5)	1.4 (1.3)	1.4 (0.5)	1.5 (0.6)
	Min , Max	0.3 , 3.0	0.3 , 2.8	0.3 , 3.0	0.3 , 2.9	0.4 , 3.0
	Median (Q1 , Q3)	1.4 (1.0 , 1.8)	1.3 (1.0 , 1.7)	1.5 (1.1 , 1.9)	1.3 (1.0 , 1.7)	1.5 (1.1 , 2.0)
Planned endocrine therapy	Yes	160 (14%)	23 (8%)	55 (21%)	26 (8%)	56 (21%)
	No	987 (86%)	283 (92%)	213 (79%)	283 (92%)	208 (79%)

Supplementary Table E. Patient-reported outcome (PRO) compliance and missing data rates for patients recruited at non-EORTC sites[a] for Breast Cancer Treatment Outcome Scale (BCTOS), Body Image Scale (BIS), Cancer Worry Scale (CWS); (n=968 patients recruited to the BIG 3-07 trial at non-EORTC sites June 2007 – 14 August 2013)

	PRO data collection time-point	Number of patients recruited to HRQOL study at non-EORTC sites and still on study (N) at HRQOL data collection time-point			Number compliant with planned HRQOL questionnaires (N)			HRQOL missing data rates[b] (%)		
		No boost	Boost	Total	No boost	Boost	Total	No boost	Boost	Total
BCTOS	Baseline	484	483	967	459	461	920	5.2 %	4.6 %	4.9 %
	End of RT	479	472	951	441	444	885	7.9 %	5.9 %	6.9 %
	6 months post RT	474	462	936	426	429	855	10 %	7.1 %	8.7 %
	12 months post RT	468	460	928	423	426	849	9.6 %	7.4 %	8.5 %
	24 months post RT	457	461	918	408	417	825	11 %	9.5 %	10 %
BIS	Baseline	484	483	967	459	460	919	5.2 %	4.8 %	5.0 %
	End of RT	479	472	951	441	444	885	7.9 %	5.9 %	6.9 %
	6 months post RT	474	462	936	427	429	856	9.9 %	7.1 %	8.5 %
	12 months post RT	468	460	928	424	426	850	9.4 %	7.4 %	8.4 %
	24 months post RT	457	461	918	409	417	826	11 %	9.5 %	10 %
CWS	Baseline	484	483	967	452	456	908	6.6 %	5.6 %	6.1 %
	End of RT	479	472	951	435	441	876	9.2 %	6.6 %	7.9 %
	6 months post RT	474	462	936	419	426	845	12 %	7.8 %	9.7 %
	12 months post RT	468	460	928	416	423	839	11 %	8.0 %	9.6 %
	24 months post RT	457	461	918	403	413	816	12 %	10 %	11 %
Perceived Risk	Baseline	484	483	967	441	437	878	8.9 %	9.5%	9.2%
	End of RT	479	472	951	418	420	838	13 %	11 %	12 %
	6 months post RT	474	462	936	401	409	810	15 %	11 %	13 %
	12 months post RT	468	460	928	403	406	809	14 %	12 %	13 %
	24 months post RT	457	461	918	389	396	785	15 %	14 %	14 %

a. The 240 substudy participants from EORTC sites completed the QLQ-C30 questionnaire only; 44 patients from European centres that were not EORTC centres completed all PRO questionnaires.

b. Missing data % calcaultes as 100% minus compliance (%) with the planned PRO assessment schedule, calculated for each PRO data collection time point as the proportion of those still-on-study patients.

Supplementary Table F. Patient characteristics at baseline for patients included in analysis: boost vs no boost (n=1147[a]), by those with and without 2 year visit quality of life data

		Have 2 year data		Do not have 2 year data	
		No boost (N=492)	**Boost (N=496)**	**No boost (N=82)**	**Boost (N=77)**
Age	<50	87 (18%)	86 (17%)	15 (18%)	19 (25%)
	≥50	405 (82%)	410 (83%)	67 (82%)	58 (75%)
Region	Australia, New Zealand, Singapore	188 (38%)	194 (39%)	24 (29%)	21 (27%)
	Canada	105 (21%)	107 (22%)	12 (15%)	9 (12%)
	UK, Ireland	96 (20%)	94 (19%)	14 (17%)	16 (21%)
	Europe	103 (21%)	101 (20%)	32 (39%)	31 (40%)
Tumour location	Upper outer quadrant	169 (34%)	188 (38%)	32 (40%)	31 (40%)
	Upper inner quadrant	57 (12%)	46 (9%)	3 (4%)	6 (8%)
	3 o'clock	27 (5%)	42 (8%)	5 (6%)	3 (4%)
	12 o'clock	46 (9%)	37 (7%)	4 (5%)	2 (3%)
	Central (within 3cm radius of nipple)	54 (11%)	77 (16%)	11 (14%)	14 (18%)
	Lower inner quadrant	33 (7%)	26 (5%)	2 (2%)	6 (8%)
	Lower outer quadrant	50 (10%)	32 (6%)	12 (15%)	6 (8%)
	6 o'clock	22 (4%)	22 (4%)	5 (6%)	2 (3%)
	9 o'clock	34 (7%)	26 (5%)	7 (9%)	7 (9%)
Number of re-excisions following initial surgery	0	333 (68%)	327 (66%)	62 (76%)	55 (71%)
	1	148 (30%)	150 (30%)	18 (22%)	20 (26%)
	2	6 (1%)	14 (3%)	1 (1%)	2 (3%)
	3	3 (1%)	0 (0%)	0 (0%)	0 (0%)
	At least 1	2 (0%)	4 (1%)	1 (1%)	0 (0%)
	Unknown	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Sentinel Node Biopsy[b]	Yes	103 (21%)	98 (20%)	24 (29%)	23 (30%)
	No	389 (79%)	398 (80%)	58 (71%)	54 (70%)

		Have 2 year data		Do not have 2 year data	
		No boost (N=492)	**Boost (N=496)**	**No boost (N=82)**	**Boost (N=77)**
Axillary Dissection	Yes	6 (1%)	12 (2%)	2 (2%)	1 (1%)
	No	486 (99%)	484 (98%)	80 (98%)	76 (99%)
Microscopic tumour size	Less than or equal to 20mm	309 (63%)	316 (64%)	49 (60%)	52 (68%)
	21mm to 50mm	152 (31%)	148 (30%)	20 (24%)	17 (22%)
	Greater than 50mm	20 (4%)	19 (4%)	5 (6%)	5 (6%)
	Unknown	11 (2%)	13 (3%)	8 (10%)	3 (4%)
Months from surgery to randomisation	Mean (s.d.)	1.4 (1.0)	1.4 (0.5)	1.4 (0.5)	1.5 (0.6)
	Min , Max	0.3 , 3.0	0.3 , 3.0	0.5 , 2.7	0.3 , 2.8
	Median (Q1 , Q3)	1.4 (1.0 , 1.8)	1.4 (1.0 , 1.8)	1.3 (1.0 , 1.7)	1.4 (1.0 , 1.8)
Planned endocrine therapy	Yes	64 (13%)	69 (14%)	14 (17%)	13 (17%)
	No	428 (87%)	427 (86%)	68 (83%)	a 83%)

a. These 1147 patients completed measures at baseline and at least one other time point reported.

b. P-value for test of association between having or not having 2 year data and sentinel node biopsy was 0.009 (Pearson chi-squared test)

Supplementary Table G. Error! No text of specified style in document. Patient-reported outcome (PRO) scores a3t baseline and two years, by sentinel node biopsy at baseline (Yes, No), for patients who completed PRO questionnaires are baseline and two years (n=988)

			Sentinel Node Biopsy		Wilcoxon Test
		Total	**No**	**Yes**	**P-Value**
EORTC QLQ-C30 mean (SD)		(N=988)	(N=787)	(N=201)	
Physical functioning	Baseline	91.91 (11.68)	92.39 (11.55)	90.03 (12.01)	0.001
(0-100, higher indicates better function)	2 years	90.78 (13.57)	91.22 (13.27)	89.09 (14.60)	0.042
	Difference	-1.20 (12.37)	-1.27 (12.52)	-0.94 (11.78)	0.88
Fatigue	Baseline	19.03 (17.89)	18.50 (17.55)	21.06 (19.03)	0.088
(0-100, higher indicates more fatigue)	2 years	18.35 (20.22)	17.75 (19.62)	20.67 (22.27)	0.13
	Difference	-0.69 (20.51)	-0.77 (19.98)	-0.39 (22.53)	0.78
Breast Cancer Treatment Outcome Scale mean (SD)		(N=819)	(N=698)	(N=121)	
Functional status	Baseline	1.24 (0.45)	1.20 (0.41)	1.44 (0.57)	<0.001
(1-4, higher indicates greater perceived difference between the treated and untreated breast and area)	2 years	1.29 (0.55)	1.27 (0.52)	1.44 (0.65)	<0.001
	Difference	0.05 (0.58)	0.06 (0.57)	0.00 (0.64)	0.32
Cosmetic status	Baseline	1.76 (0.54)	1.74 (0.53)	1.88 (0.55)	<0.001
(1-4, higher indicates greater perceived difference between the treated and untreated breast and area)	2 years	1.83 (0.58)	1.81 (0.58)	1.99 (0.57)	<0.001
	Difference	0.07 (0.56)	0.07 (0.56)	0.10 (0.58)	0.77
Breast-specific pain	Baseline	1.83 (0.66)	1.82 (0.64)	1.87 (0.74)	0.65
(1-4, higher indicates greater perceived difference between the treated and untreated breast and area)	2 years	1.71 (0.69)	1.71 (0.70)	1.74 (0.67)	0.42
	Difference	-0.12 (0.75)	-0.11 (0.75)	-0.14 (0.79)	0.60
Body Image Scale mean (SD)		(N=820)	(N=699)	(N=121)	
(0-30, higher indicates more symptoms/distress)	Baseline	2.50 (4.35)	2.42 (4.39)	2.96 (4.11)	0.006
	2 years	2.56 (4.64)	2.45 (4.54)	3.19 (5.15)	0.090
	Difference	0.06 (4.24)	0.03 (4.18)	0.23 (4.57)	0.71
Cancer Worry Scale mean (SD)		(N=810)	(N=691)	(N=119)	
(0-16, higher indicates more more cancer worry)	Baseline	7.07 (2.42)	7.05 (2.34)	7.18 (2.86)	0.74
	2 years	6.24 (2.09)	6.20 (2.06)	6.46 (2.24)	0.26
	Difference	-0.82 (2.20)	-0.84 (2.20)	-0.71 (2.21)	0.40
Perceived risk (5 categories)					
Baseline	Much lower	163 (21%)	137 (20%)	26 (23%)	0.72
	Somewhat lower	141 (18%)	125 (19%)	16 (14%)	
	The same	354 (45%)	305 (46%)	49 (44%)	
	Somewhat higher	106 (14%)	88 (13%)	18 (16%)	
	Much higher	18 (2%)	15 (2%)	3 (3%)	
2 years	Much lower	138 (18%)	113 (17%)	25 (22%)	0.70
	Somewhat lower	127 (16%)	114 (17%)	13 (12%)	
	The same	396 (50%)	340 (51%)	56 (50%)	
	Somewhat higher	105 (13%)	88 (13%)	17 (15%)	
	Much higher	19 (2%)	18 (3%)	1 (1%)	
Difference	-4	3 (0%)	3 (0%)	0 (0%)	0.62
	-3	5 (1%)	3 (0%)	2 (2%)	
	-2	51 (7%)	41 (6%)	10 (9%)	
	-1	119 (16%)	102 (16%)	17 (16%)	
	0	360 (47%)	315 (48%)	45 (42%)	
	1	139 (18%)	117 (18%)	22 (21%)	
	2	73 (10%)	63 (10%)	10 (9%)	
	3	11 (1%)	10 (2%)	1 (1%)	

Supplementary Table H. Correlations among 8 key patient-reported outcomes (PROs) at each PRO assessment timepoint (Spearman's rank correlation coefficient).

	Fatigue	Physical functioning	Functional status	Cosmetic status	Breast-specific pain	Body image scale	Cancer worry scale	Perceived risk
Baseline measures								
Fatigue	1.00	-0.50	0.36	0.20	0.33	0.25	0.21	0.08
Physical functioning	-0.50	1.00	-0.34	-0.11	-0.17	-0.15	-0.12	-0.06
Functional status (1-4)	0.36	-0.34	1.00	0.24	0.39	0.27	0.25	0.07
Cosmetic status (1-4)	0.20	-0.11	0.24	1.00	0.46	0.52	0.20	0.16
Breast-specific pain (1-4)	0.33	-0.17	0.39	0.46	1.00	0.35	0.29	0.13
Body image scale (0-30)	0.25	-0.15	0.27	0.52	0.35	1.00	0.36	0.16
Cancer worry scale (0-16)	0.21	-0.12	0.25	0.20	0.29	0.36	1.00	0.30
Perceived risk (5 categories)	0.08	-0.06	0.07	0.16	0.13	0.16	0.30	1.00
End of RT								
Fatigue	1.00	-0.62	0.45	0.35	0.47	0.32	0.21	0.07
Physical functioning	-0.62	1.00	-0.52	-0.29	-0.36	-0.27	-0.15	-0.07
Functional status (1-4)	0.45	-0.52	1.00	0.36	0.40	0.32	0.23	0.05
Cosmetic status (1-4)	0.35	-0.29	0.36	1.00	0.60	0.50	0.25	0.15
Breast-specific pain (1-4)	0.47	-0.36	0.40	0.60	1.00	0.37	0.23	0.13
Body image scale (0-30)	0.32	-0.27	0.32	0.50	0.37	1.00	0.42	0.18
Cancer worry scale (0-16)	0.21	-0.15	0.23	0.25	0.23	0.42	1.00	0.30
Perceived risk (5 categories)	0.07	-0.07	0.05	0.15	0.13	0.18	0.30	1.00
6 months								
Fatigue	1.00	-0.61	0.40	0.21	0.35	0.25	0.26	0.10
Physical functioning	-0.61	1.00	-0.45	-0.23	-0.28	-0.23	-0.22	-0.08
Functional status (1-4)	0.40	-0.45	1.00	0.29	0.38	0.27	0.26	0.05
Cosmetic status (1-4)	0.21	-0.23	0.29	1.00	0.52	0.55	0.31	0.17
Breast-specific pain (1-4)	0.35	-0.28	0.38	0.52	1.00	0.38	0.38	0.13
Body image scale (0-30)	0.25	-0.23	0.27	0.55	0.38	1.00	0.38	0.17
Cancer worry scale (0-16)	0.26	-0.22	0.26	0.31	0.38	0.38	1.00	0.27
Perceived risk (5 categories)	0.10	-0.08	0.05	0.17	0.13	0.17	0.27	1.00

	Fatigue	Physical functioning	Functional status	Cosmetic status	Breast-specific pain	Body image scale	Cancer worry scale	Perceived risk
12 months								
Fatigue	1.00	-0.61	0.34	0.22	0.36	0.26	0.26	0.06
Physical functioning	-0.61	1.00	-0.40	-0.19	-0.29	-0.24	-0.15	0.02
Functional status (1-4)	0.34	-0.40	1.00	0.30	0.40	0.29	0.24	0.06
Cosmetic status (1-4)	0.22	-0.19	0.30	1.00	0.47	0.51	0.25	0.16
Breast-specific pain (1-4)	0.36	-0.29	0.40	0.47	1.00	0.33	0.31	0.12
Body image scale (0-30)	0.26	-0.24	0.29	0.51	0.33	1.00	0.39	0.13
Cancer worry scale (0-16)	0.26	-0.15	0.24	0.25	0.31	0.39	1.00	0.29
Perceived risk (5 categories)	0.06	0.02	0.06	0.16	0.12	0.13	0.29	1.00
2 years								
Fatigue	1.00	-0.60	0.34	0.23	0.32	0.29	0.26	0.08
Physical functioning	-0.60	1.00	-0.39	-0.17	-0.21	-0.18	-0.18	-0.05
Functional status (1-4)	0.34	-0.39	1.00	0.28	0.37	0.33	0.24	0.03
Cosmetic status (1-4)	0.23	-0.17	0.28	1.00	0.41	0.55	0.19	0.09
Breast-specific pain (1-4)	0.32	-0.21	0.37	0.41	1.00	0.38	0.27	0.11
Body image scale (0-30)	0.29	-0.18	0.33	0.55	0.38	1.00	0.37	0.10
Cancer worry scale (0-16)	0.26	-0.18	0.24	0.19	0.27	0.37	1.00	0.26
Perceived risk (5 categories)	0.08	-0.05	0.03	0.09	0.11	0.10	0.26	1.00

Supplementary Table I. Patient-reported outcome summaries at baseline by geographic region

			Region				
		Total (N=1147)	**AU, NZ, SG* (N=427)**	**Canada (N=233)**	**UK, Ireland (N=220)**	**Europe (N=267)**	**Kruskal-Wallis p-value**
EORTC QLQ-C30							
Physical functioning	N	1,147	427	233	220	267	0.011
	Mean (s.d.)	91.7 (12.1)	93.0 (10.6)	91.6 (10.7)	91.4 (12.3)	89.7 (14.7)	
Fatigue	N	1,146	426	233	220	267	0.24
	Mean (s.d.)	19.3 (18.6)	17.8 (16.7)	19.4 (19.0)	18.6 (18.2)	22.0 (21.2)	
BCTOS							
Functional status (1-4)	N	919	427	233	216	43	0.21
	Mean (s.d.)	1.24 (0.45)	1.22 (0.44)	1.22 (0.42)	1.30 (0.52)	1.22 (0.37)	
Cosmetic status (1-4)	N	918	425	233	217	43	0.008
	Mean (s.d.)	1.77 (0.55)	1.77 (0.52)	1.74 (0.54)	1.77 (0.59)	2.05 (0.61)	
Breast-specific symptoms (1-4)	N	920	427	233	217	43	0.46
	Mean (s.d.)	1.84 (0.67)	1.83 (0.68)	1.81 (0.63)	1.86 (0.68)	1.97 (0.68)	
Body image scale (0-30)	N	919	426	233	217	43	<0.001
	Mean (s.d.)	2.64 (4.45)	2.12 (3.94)	2.90 (4.33)	3.03 (5.22)	4.54 (4.92)	
Cancer worry scale (0-16)	N	908	425	224	216	43	0.023
	Mean (s.d.)	7.13 (2.47)	7.01 (2.38)	6.88 (2.35)	7.57 (2.72)	7.30 (2.42)	
Perceived risk (5 categories)	N	878	412	217	208	41	0.35
	Much lower	172 (20%)	81 (20%)	53 (24%)	33 (16%)	5 (12%)	
	Somewhat lower	157 (18%)	67 (16%)	40 (18%)	43 (21%)	7 (17%)	
	The same	407 (46%)	193 (47%)	90 (41%)	98 (47%)	26 (63%)	
	Somewhat higher	121 (14%)	58 (14%)	32 (15%)	28 (13%)	3 (7%)	
	Much higher	21 (2%)	13 (3%)	2 (1%)	6 (3%)	0 (0%)	

EORTC QLQ-C30: A high score for physical functioning represents a high level of functions, but a high score fatigue represents a more fatigue.
BCTOS: A higher score indicates greater perceived difference between the treated and untreated breast and area.
BIS: A higher score represents more symptoms/distress.
CWS: A higher cancer worry scale indicates more cancer worries.
Perceived risk: In your opinion, compared with other women your age who have DCIS, what are your chances of getting invasive breast cancer

List of BIG 3-07/TROG 07.01 principal investigators and sites which recruited patients to the Quality of Life substudy

Site	Country	Percentage of patients who participated in PRO	Total number of DCIS patients per site	Principal Investigator
Peter MacCallum Cancer Centre	Australia	83%	90	Boon H Chua Claire Phillips
Radiation Oncology Services Mater Centre	Australia	87%	78	Guy Bryant
Arnhems Radiotherapeutisch Instituut - ARTI	Netherlands	83%	66	Helen Westenberg
Sheffield Teaching Hospitals	UK	68%	66	O P Purohit
Westmead Hospital	Australia	84%	63	Verity Ahern
St George Hospital	Australia	89%	44	Peter Graham
Cancer Care Manitoba	Canada	81%	43	Mohamed Akra
SLRON at SLH SJH and Beaumont	Ireland	63%	38	Orla McArdle
Calvary Mater Newcastle	Australia	91%	34	Peter O'Brien Jane Ludbrook
Princess Alexandra Hospital	Australia	75%	32	Jennifer Harvey
University Medical Centre Groningen	Netherlands	74%	31	John H. Maduro
Chr De Grenoble - La Tronche	France	77%	30	Isabelle Gabelle-Flandin
Cliniques Universitaires St Luc	Belgium	67%	30	Carine Kirkove
Edinburgh Western General Hospital	UK	59%	29	Carolyn Bedi
University Hospital Galway	Ireland	77%	26	Joseph Martin
Notre Dame Hospital	Canada	96%	25	Tony Vu
McGill University Department of Oncology	Canada	84%	25	Theirry Muanza
Royal Surrey County Hospital	UK	64%	25	Anthony Neal
Centre Antoine Lacassagne	France	67%	24	Adel Courdi Juliette Thariat
Odette Cancer Centre -	Canada	87%	23	Eileen Rakovitch
Leiden University Medical Centre	Netherlands	73%	22	Laurien Daniels Marjan van Hezewijk
Nova Scotia Cancer Centre	Canada	95%	21	Wlasyslawa Cwajna
Onze Lieve Vrouw Ziekenhuis	Belgium	81%	21	Adelheid Roelstraete
Maastricht Radiation Oncology - Maastro Clinic	Netherlands	67%	21	Angela van Baardwijk
Cancer Institute Antoni Van Leeuwenhoekziekenhuis	Netherlands	75%	20	Nicola Russel
Princess Margaret Hospital	Canada	65%	20	Anne Koch Jennifer Croke
Royal Marsden Hospital	UK	72%	18	Imogen Locke
Riverina Cancer Care Centre	Australia	94%	16	Peter Jeal Quenten Walker Kandeepeepan Thuraisingham Anupam Chauduri
Sir Charles Gairdner Hospital	Australia	75%	16	David Joseph Mandy Taylor
ZNA Middelheim	Belgium	56%	16	Sabine Vanderkam
National University Hospital	Singapore	100%	15	Tony Woo Johann Tang
Hopital Maisonneuve-Rosemont	Canada	100%	15	Michael Yassa
Vancouver Island Cancer Centre	Canada	93%	15	Elaine Wai
The Townsville Hospital	Australia	87%	15	Susan Hewitt
Allan Blair Cancer Centre	Canada	80%	15	Shazia Mahmood
Cork University Hospital	Ireland	47%	15	Jennifer Gilmore Bolante Ofi
University Hospitals Bristol NHS Foundation Trust	UK	33%	15	Amit Bahl
London Regional Cancer Program	Canada	100%	14	Olga Vujovic Edward Yu
Saskatoon Cancer Centre	Canada	64%	14	Duc Le
Jurvanski Cancer Centre	Canada	21%	14	Iwa Kong
BCCA Vancouver Centre	Canada	85%	13	Alan Nichol
Academisch Medisch Centrum	Netherlands	69%	13	N. Bijker
Liverpool Hospital	Australia	62%	13	Geoff Delaney
Austin Hospital	Australia	100%	12	Malcolm Feigen Adeline Lim Michael Chao
Royal Perth Hospital	Australia	100%	12	Dr Margaret Latham
Southend University Hospital	UK	58%	12	Hafiz Algurafi
Brust-Zentrum Zurich-Seefeld	Switzerland	100%	11	Christoph Tausch
Toowoomba Cancer Research Centre	Australia	91%	11	Eric Khoo Sam Leung
Alfred Hospital	Australia	73%	11	Karen Taylor Sasha Senthi
University Hospital Birmingham NHS Foundation Trust	UK	73%	11	Andrea Stevens
Lincoln County Hospital	UK	64%	11	Abhro Chaudhuri
Charing Cross Hospital	UK	46%	11	Susan Cleator

University Hospital of North Staffordshire	UK	27%	11	Adrian Murray Brunt
Christchurch Hospital	New Zealand	100%	10	Scott Babington
Genesis Cancer Care - Tugun	Australia	90%	10	David Christie
Kantonsspital Graubunden	Switzerland	70%	10	Daniel Zwahlen
University Hospital Basel	Switzerland	78%	9	Ulrich Schratzenstaller
Centre Hospitalier Universitaire de Sherbrooke	Canada	67%	9	Laurence Masson
James Cook University Hospital	UK	67%	9	Nicola Storey
Saint John Regional Hospital	Canada	75%	8	Eshwar Kumar
Ipswich Hospital	UK	75%	8	Liz Sherwin
Algemeen Ziekenhuis Sint-Augustinus	Belgium	63%	8	Reinhilde Weytjens
Aberdeen Royal Infirmary	UK	63%	8	Sharma Ravi
Nottingham University Hospitals	UK	38%	8	Patricia Lawton
Waikato Hospital	New Zealand	100%	7	Ruth Angell Glenys Round Angela Allen Ziad Thotathil
Thunder Bay Regional Health Sciences Centre	Canada	100%	7	Margaret Anthes
Kantonsspital Munsterlingen	Switzerland	71%	7	Christiane Reuter
New Cross Hospital Wolverhampton	UK	57%	7	Laura Pettit
Mid Staffordshire NHS Foundation Trust, Stafford Hospital	UK	43%	7	Laura Pettit
Perth Radiation Oncology	Australia	100%	6	Yvonne Zissiadis
Auckland Hospital	New Zealand	100%	6	Christine Elder
Medisch Centrum Haaglanden Westeinde	Netherlands	100%	6	Antoinette Verbeek-de Kanter
Leon Richard Oncology Centre	Canada	83%	6	Andree Lirette
Kantonsspital St. Gallen	Switzerland	80%	5	Ludwig Plasswilm
Sandwell and West Birmingham Hospitals NHS Trust	UK	80%	5	David Spooner Fiona Hoar
Southern Interior	Canada	60%	5	Islam Mohamed
Inselspital Bern	Switzerland	60%	5	Kristina Lossl
Essex County Hospital, Colchester	UK	60%	5	Vivienne Loo
Istituto Oncologico della Svizzera Italiana (IOSI)	Switzerland	40%	5	Antonella Richetti
Dumfries & Galloway Royal Infirmary	UK	40%	5	Tamasin Evans Aisling Hennessy
Lakeridge Health Oshawa	Canada	25%	5	Medhat El-Mallah
Royal Hobart Hospital	Australia	100%	4	Marketa Skala Raef Awad
L'Hotel-Dieu de Quebec	Canada	100%	4	Isabelle Germain
Hopital de Jolimont	Belgium	100%	4	Carine Mitine
Universitair Ziekenhuis Brussel	Belgium	100%	4	Hilde Van Parijs
Worcestershire Acute Hosapitals NHS Trust, Kidderminster NHS Treatment Centre	UK	100%	4	Mark Churn
Warwick Hospital	UK	25%	4	Nawaz Walji
Barwon Health	Australia	100%	3	Michael Francis
AZ Groeninghe – Campus Maria’s Voorzienigheid	Belgium	100%	3	Karin Stellamans
Klinik Hirslanden	Switzerland	100%	3	Gunther Gruber
Fondazione Salvatore Maugeri Pavia	Italy	100%	3	Giovanni Ivaldi
Beatson West of Scotland Cancer Centre	UK	100%	3	Abdulla Alhasso
Royal Brisbane and Womens Hospital	Australia	67%	3	Lizbeth Kenny
Nepean Cancer Care Centre	Australia	67%	3	Ken Tiver
Kings Mill Hospital, Nottingham	UK	33%	3	Matthew Griffin
Royal North Shore	Australia	100%	2	Gillian Lamoury
Centro Di Riferimento Oncologico Aviano	Italy	100%	2	Marco Trovo
Basildon Hospital	UK	100%	2	Hafiz Algufarfi
Arden Cancer Research Centre Coventry	UK	100%	2	Nawaz Walji
Genesis Cancer Care - Wesley	Australia	50%	2	Minjae Lah David Christie
Royal Alexandra Hospital, Paisley	UK	50%	2	Abdulla Alhasso
Royal Adelaide Hospital	Australia	100%	1	Scott Carruthers
Campbelltown Hospital	Australia	100%	1	George Papadatos
ISALA Klinieken	Netherlands	100%	1	Gabriel Paardekooper
Pilgrim Hospital	UK	100%	1	Abhro Chaudhuri
Queen's Hospital Burton	UK	100%	1	Mojca Persic
Churchill Hospital Oxford	UK	100%	1	Bernadette Lavery